# Synthesis and Spectra of New 3-Carbethoxypyrazole Sulfonylurea Derivatives

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The reaction of 1-benzenesulfonyl-3-ethoxycarbonyl-5-[α-substituted-styryl]pyrazoles (**1**) with isocyanate and thioisocyanate derivatives yield the corresponding benzenesulfonylurea derivatives (**2** and **3**). Bromination of **1** afforded the 4-bromopyrazoles **4** which react with isocyanate derivatives giving **5** that were also obtained by bromination of **2**. Alkaline hydrolysis of the benzensulfonylurea derivatives **2** yield the corresponding pyrazole-3-carboxylic acids **7**.

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It has been reported that pyrazole-3-carboxylic acids possess high hypoglycemic activity (1-5). In this report many new substituted pyrazolesulfonylurea derivatives were synthesised in the hope that they may be of potential antidiabetic or antibacterial value.

The pyrazole esters **1** were prepared by the condensation of the appropriate δ-substituted ethyl 2,4-dioxo-6-phenyl hex-5-enoate with *p*-sulfamylhydrazine (6,7). These trisubstituted pyrazoles upon reaction with the appropriate isocyanate or thioisocyanate in dry acetone (8) afforded the corresponding *p*-(3-ethoxycarbonyl-5-[α-substituted-styryl]-1-pyrazolyl)benzenesulfonylurea derivatives (**2**) and substituted *p*-(3-ethoxycarbonyl-5-[α-substituted-styryl]-1-pyrazolyl)-benzenesulfonylthiourea derivatives (**3**).

The ir absorption spectra of these trisubstituted pyrazoles (**2,3**) showed an absorption band at 1700-1725 $cm^{-1}$ due to the carbonyl of the ester group and two bands at 1330-1350 $cm^{-1}$ and 1170-1190 $cm^{-1}$ due to the $-SO_2N<$ group. In addition to the above mentioned bands, the ir spectra of the pyrazoles (**2**) showed another carbonyl band at 1650-1660 $cm^{-1}$ of the amide group.

It is worthy to mention that in the $^1H$ nmr spectra of the above pyrazole derivatives, generally no separate signals could be assigned for C-4 protons of the pyrazole ring. These protons usually resonate in the same region as the complex multiplet of the side chain aromatic protons (9).

Bromination of the trisubstituted pyrazoles **1** in

Scheme

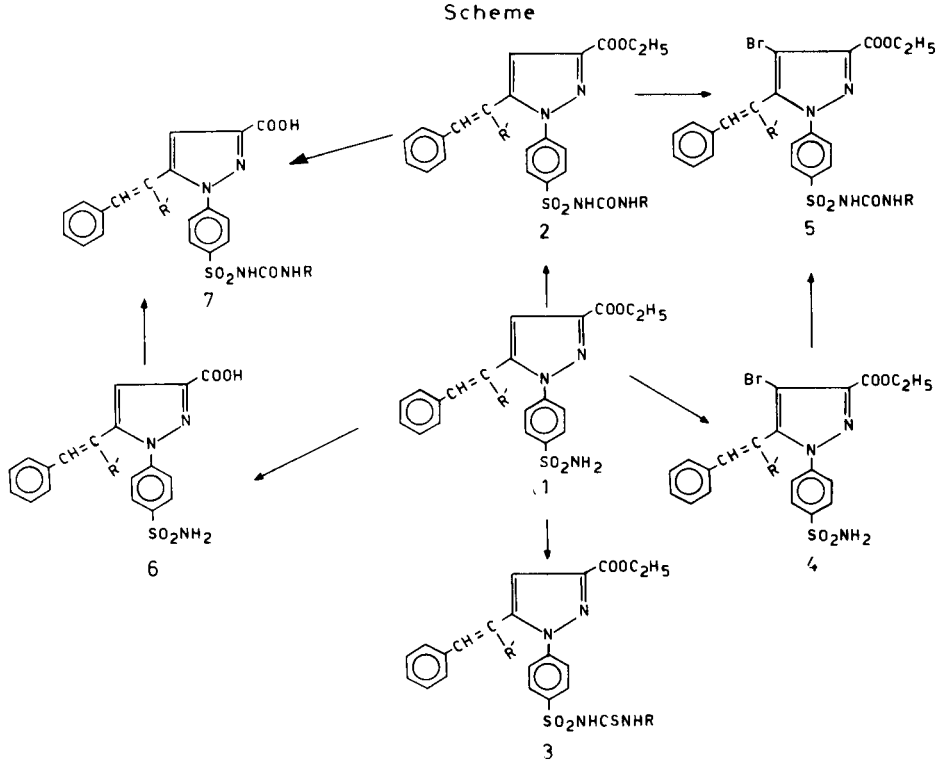

Table I:
Substituted *p*-(3-Ethoxycarbonyl-5-[α-substituted-styryl]-1-pyrazolyl)benzenesulfonylurea and Thiourea Derivatives

| Compound | R' | R | Yield % | M.p. °C | Formula | Analysis C | H | Calcd./found % N | S |
|---|---|---|---|---|---|---|---|---|---|
| **2a** | H | $C_2H_5$ | 5 | 160 | $C_{23}H_{24}N_4O_5S$ | 58.96 | 5.16 | 11.95 | 6.84 |
| | | | | | | 59.1 | 5.3 | 11.7 | 7.0 |
| **2b** | H | $(CH_2)_3CH_3$ | 80 | 205 | $C_{25}H_{28}N_4O_5S$ | 60.46 | 5.68 | 11.28 | 6.45 |
| | | | | | | 60.3 | 5.7 | 11.4 | 6.2 |
| **2c** | H | $C_6H_{11}$ | 80 | 185 | $C_{27}H_{30}N_4O_5S$ | 62.5 | 5.78 | 10.72 | 6.13 |
| | | | | | | 62.3 | 5.9 | 10.4 | 6.1 |
| **2d** | H | $C_6H_5$ | 70 | 200 | $C_{27}H_{24}N_4O_5S$ | 62.77 | 4.68 | 10.84 | 6.20 |
| | | | | | | 63.0 | 4.3 | 10.7 | 6.1 |
| **2e** | $CH_3$ | $C_2H_5$ | 80 | 126 | $C_{24}H_{26}N_4O_5S$ | 59.73 | 5.43 | 11.61 | 6.64 |
| | | | | | | 59.6 | 5.3 | 11.4 | 6.5 |
| **2f** | $CH_3$ | $(CH_2)_3CH_3$ | 75 | 160 | $C_{26}H_{30}N_4O_5S$ | 61.15 | 5.92 | 10.97 | 6.27 |
| | | | | | | 61.2 | 5,8 | 10.7 | 6.2 |
| **2g** | $CH_3$ | $C_6H_{11}$ | 80 | 225 | $C_{28}H_{32}N_4O_5S$ | 62.66 | 6.01 | 10.43 | 5.97 |
| | | | | | | 62.5 | 6.3 | 10.2 | 6.2 |
| **2h** | $CH_3$ | $C_6H_5$ | 75 | 229 | $C_{28}H_{26}N_4O_5S$ | 63.38 | 4.93 | 10.55 | 6.04 |
| | | | | | | 63.5 | 4.7 | 10.6 | 6.2 |
| **2i** | $C_6H_5$ | $C_2H_5$ | 80 | 198 | $C_{29}H_{28}N_4O_5S$ | 63.95 | 5.18 | 10.28 | 5.88 |
| | | | | | | 63.7 | 5.4 | 10.5 | 6.1 |
| **2j** | $C_6H_5$ | $(CH_2)_3CH_3$ | 75 | 128 | $C_{31}H_{32}N_4O_5S$ | 65.01 | 5.63 | 9.78 | 5.59 |
| | | | | | | 65.0 | 5.7 | 9.8 | 5.6 |
| **2k** | $C_6H_5$ | $C_6H_{11}$ | 75 | 235 | $C_{33}H_{34}N_4O_5S$ | 66.20 | 5.72 | 9.35 | 5.35 |
| | | | | | | 66.2 | 5.8 | 9.5 | 5.2 |
| **2l** | $C_6H_5$ | $C_6H_5$ | 70 | 205 | $C_{33}H_{28}N_4O_8S$ | 66.87 | 4.76 | 9.45 | 5.41 |
| | | | | | | 67.0 | 4.6 | 9.7 | 5.3 |
| **3a** | H | $C_2H_5$ | 60 | 260 | $C_{23}H_{24}N_4O_4S_2$ | 57.00 | 4.99 | 11.56 | 13.23 |
| | | | | | | 57.3 | 5.2 | 11.4 | 13.4 |
| **3b** | $CH_3$ | $C_2H_5$ | 70 | 158 | $C_{24}H_{26}N_4O_4S_2$ | 57.81 | 5.25 | 11.25 | 12.86 |
| | | | | | | 57.6 | 5.3 | 11.4 | 12.8 |
| **3c** | $CH_3$ | $(CH_2)_3CH_3$ | 75 | 159 | $C_{26}H_{30}N_4O_4S_2$ | 59.29 | 5.74 | 10.63 | 12.17 |
| | | | | | | 59.3 | 5.8 | 10.8 | 12.4 |
| **3d** | $CH_3$ | $C_6H_{11}$ | 80 | 199 | $C_{28}H_{32}N_4O_4S_2$ | 60.84 | 5.83 | 10.13 | 11.60 |
| | | | | | | 60.7 | 5.7 | 10.2 | 11.4 |
| **3e** | $CH_3$ | $C_6H_5CH_2$ | 75 | 179 | $C_{29}H_{28}N_4O_4S_2$ | 62.12 | 5.03 | 9.99 | 11.43 |
| | | | | | | 62.3 | 5.1 | 10.1 | 11.6 |
| **3f** | $C_6H_5$ | $C_2H_5$ | 85 | 186 | $C_{29}H_{28}N$ | 62.12 | 5.03 | 9.99 | 11.43 |
| | | | | | | 62.3 | 5.2 | 9.7 | 11.3 |
| **3g** | $C_6H_5$ | $C_6H_{11}$ | 80 | 120 | $C_{33}H_{34}N_4O_4S_2$ | 64.47 | 5.57 | 9.11 | 10.43 |
| | | | | | | 64.2 | 5.6 | 9.3 | 10.2 |

chloroform afforded the corresponding 4-bromopyrazoles **4** which upon reaction with substituted isocyanates yielded the substituted pyrazolesulfonylurea derivatives **5**. That were also obtained from the bromination of **2**.

The ir spectra of the 4-bromopyrazole esters **4** showed the two bands of the $NH_2$ group at 3170 and 3350 $cm^{-1}$ as well as the carbonyl ester band at 1720-1730 $cm^{-1}$.

The $^1H$ nmr spectrum of the 4-bromopyrazole (**4q**) exhibited besides the aromatic and ethyl ester protons, two doublets (J = 5 Hz) at δ 5.2 and 5.5 for the C-α and C-β protons, respectively. On the other hand the $^1H$ nmr spectra of the pyrazoles **4b** and **4c** lacked the signal of the C-α proton and showed a signal at δ 5.1-5.2 for the C-β proton.

Alkaline hydrolysis of the pyrazole esters **1** with ethanolic 2*N* potassium hydroxide solution afforded the corresponding pyrazole-3-carboxylic acids **6** (7). The corresponding pyrazolesulfonylurea derivatives **7**, were obtained by the hydrolysis of **2** and also by reaction of **6** with cyclohexylisocyanate and phenylisocyanate, respectively.

The ir spectra of the pyrazolecarboxylic acids **7** showed two carbonyl absorption bands at 1670-1680 $cm^{-1}$ and 1645-1655 $cm^{-1}$ for the (-COOH) and (-CONH-) groups, respectively. In addition to the above mentioned bands an absorption band appeared at 3350 $cm^{-1}$ due to the hydroxyl group.

The $^1H$ nmr spectra of the pyrazolecarboxylic acids **6** and **7** exhibited besides the aromatic protons, an exchangeable COOH signal at δ 10.6-10.9.

## EXPERIMENTAL

Microanalyses were performed by the Microanalysis Unit, Cairo University, Cairo. Infrared spectra were measured with a Beckman IR-4210 Spectrophotometer in potassium bromide pellets or in Nujol and electronic spectra were measured in ethanolic solutions with a

Table II:
(i) 1-(*p*-Sulfamylphenyl)-4-bromo-3-ethoxycarbonyl-5-[α-substituted-styryl]pyrazoles (**4**)
(ii) Substituted *p*-(4-Bromo-3-ethoxycarbonyl-5-[α-substituted-styryl]-1-pyrazolylbenzenesulfonylurea Derivatives (**5**)
(iii) *p*-(3-Carboxy-5-[α-substituted-styryl]-1-pyrazolylbenezenesulfonylphenylurea (**7**)

| Compound | R′ | R | Yield % | M.p. °C | Formula | Analysis C | H | Calcd./found % N | S | Br |
|---|---|---|---|---|---|---|---|---|---|---|
| **4a** | H | | 80 | 178 | $C_{20}H_{18}BrN_3O_4S$ | 50.42 | 3.80 | 8.82 | 6.73 | 16.77 |
| | | | | | | 50.4 | 4.11 | 8.5 | 6.3 | 16.4 |
| **4b** | $CH_3$ | | 70 | 162 | $C_{21}H_{20}BrN_3O_4S$ | 51.43 | 4.11 | 8.56 | 6.53 | 16.29 |
| | | | | | | 51.6 | 4.3 | 8.7 | 6.11 | 16.3 |
| **4c** | $C_6H_5$ | | 75 | 220 | $C_{26}H_{22}BrN_3O_4S$ | 56.52 | 4.01 | 7.60 | 5.80 | 14.46 |
| | | | | | | 56.6 | 4.2 | 7.8 | 5.8 | 14.2 |
| **5a** | H | $(CH_2)_3CH_3$ | 70 | 130 | $C_{27}H_{29}BrN_4O_5S$ | 52.17 | 4.72 | 9.73 | 5.57 | 13.88 |
| | | | | | | 52.3 | 4.8 | 9.8 | 5.6 | 13.9 |
| **5b** | H | $C_6H_{11}$ | 70 | 160 | $C_{27}H_{29}BrN_4O_5S$ | 53.91 | 4.85 | 9.31 | 5.33 | 13.28 |
| | | | | | | 53.6 | 4.5 | 9.2 | 5.1 | 13.1 |
| **5c** | H | $C_6H_5$ | 65 | 240 | $C_{27}H_{23}BrN_4O_5S$ | 54.46 | 3.89 | 9.40 | 5.38 | 13.41 |
| | | | | | | 54.5 | 3.9 | 9.3 | 5.4 | 13.2 |
| **5d** | $CH_3$ | $C_6H_{11}$ | 75 | 215 | $C_{28}H_{31}BrN_4O_5S$ | 54.63 | 5.07 | 9.10 | 5.20 | 12.98 |
| | | | | | | 54.4 | 5.2 | 9.0 | 5.1 | 13.1 |
| **5e** | $CH_3$ | $C_6H_5$ | 70 | 278 | $C_{28}H_{25}BrN_4O_5S$ | 55.17 | 4.13 | 9.19 | 5.26 | 13.11 |
| | | | | | | 55.1 | 4.3 | 9.2 | 5.3 | 13.2 |
| **5f** | $C_6H_5$ | $C_2H_5$ | 75 | 158 | $C_{29}H_{27}BrN_4O_5S$ | 55.86 | 4.36 | 8.98 | 5.14 | 12.81 |
| | | | | | | 56.0 | 4.4 | 8.7 | 5.3 | 13.0 |
| **5g** | $C_6H_5$ | $(CH_2)_3CH_3$ | 70 | 162 | $C_{31}H_{31}BrN_4O_5S$ | 57.14 | 4.79 | 8.59 | 4.92 | 12.26 |
| | | | | | | 57.3 | 4.6 | 8.4 | 4.6 | 12.2 |
| **7a** | $C_6H_5$ | $C_6H_{11}$ | 70 | 210 | $C_{31}H_{30}N_4O_5S$ | 65.24 | 5.29 | 9.81 | 5.61 | |
| | | | | | | 65.3 | 5.1 | 9.8 | 5.3 | |
| **7b** | $C_6H_5$ | $C_6H_5$ | 65 | 235 | $C_{31}H_{24}N_4O_5S$ | 65.94 | 4.28 | 9.92 | 5.67 | |
| | | | | | | 66.0 | 4.2 | 10.1 | 5.8 | |

Table III:
Infrared and Electronic Spectral Data of the Pyrazole Derivatives

| Compound | Ir($cm^{-1}$) C=O ester | C=O amide | C=S | $-SO_2N<$ | λ/max, Nm, (ε) | | |
|---|---|---|---|---|---|---|---|
| **2a** | 1710 | 1650 | | 1330, 1170 | 230* (19563) | | 307 (27581) |
| **2b** | 1715 | 1655 | | 1345,1175 | 228 (16684) | 268 (20321) | 248 (25669) |
| **2c** | 1700 | 1660 | | 1340, 1178 | 230 (12636) | 270* (13689) | 300 (15795) |
| **2d** | 1715 | 1658 | | 1350, 1190 | 237 (32268) | 270* (26245) | |
| **2e** | 1710 | 1650 | | 1335, 1175 | 257 (26004) | | |
| **2f** | 1720 | 1652 | | 1330, 1170 | 258 (25726) | | |
| **2g** | 1710 | 1655 | | 1340, 1175 | 260 (22473) | | |
| **2h** | 1710 | 1660 | | 1345, 1180 | 265 (39458) | | |
| **2i** | 1715 | 1650 | | 1342, 1190 | 230 (27215) | 274 (22182) | |
| **2j** | 1710 | 1660 | | 1336, 1185 | | | |
| **2k** | 1718 | 1660 | | 1330, 1175 | 237 (36342) | 275 (34571) | 300* (34390) |
| **2l** | 1716 | 1655 | | | 242 (30080) | 252* (28229) | |
| **3a** | 1715 | | 1050 | 1330, 1170 | 263 (34605 | | |
| **3b** | 1725 | | 1100 | 1335, 1180 | | | |
| **3c** | 1705 | | 1150 | 1350, 1185 | 235 (30550) | 277 (23203) | 307* (15468) |
| **3d** | 1720 | | 1200 | 1340, 1175 | 260 (38768) | | |
| **3e** | 1715 | | 1100 | 1340, 1190 | 262 (33579) | | |
| **3f** | 1710 | | 1180 | 1350, 1170 | 230 (28200) | 275(20704) | |
| **3g** | 1718 | | 1150 | 1330, 1175 | | | |
| **4a** | 1725 | | | 1335, 1175 | 228 (17262) | 265* (11905) | |
| **4b** | 1730 | | | 1350, 1140 | 225 (14696) | 250 (15100) | |
| **4c** | 1720 | | | 1360, 1180 | 233 (29497) | 275 (27614) | |
| **5a** | 1710 | 1660 | | 1330, 1176 | | | |
| **5b** | 1730 | 1650 | | 1350, 1180 | 230 (32470) | 257 (28909) | |
| **5c** | 1720 | 1640 | | 1360, 1185 | 225 (14134) | 255* (15307) | |
| **5d** | 1725 | 1650 | | 1355, 1190 | | | |
| **5d** | 1728 | 1660 | | 1340, 1170 | 265 (53083) | | |
| **5f** | 1730 | 1660 | | 1345, 1170 | 225* (30083) | 277 (25322) | |
| **7a** | $1700_a$ | 1650 | | 1345, 1170 | 235 (126238) | 272 (11757) | |
| **7b** | $1695_a$ | 1652 | | 1340, 1180 | | | |

(a) C=O carboxylic acid. (b) The ir spectrum showed two bands at 3170, 3350 for the $NH_2$ group (*) shoulder.

Table IV:
$^1$H NMR Spectral Data of the Pyrazole Derivatives

| Compound | $CH_3$ (s) | $CH_3$ (t) (3N) | $CH_2$ (a) (2N) | $^1$H NMR Chemical Shifts (δ/ppm) A- (d) | H-B (d) | $NH_2$ | Ar-H + H-4 (m) | Others |
|---|---|---|---|---|---|---|---|---|
| **1a** | | 1.12 | 4.20 | 5.15 | 5.30 | 6.40 | 8.0 | |
| **1b** | 1.35 | 1.13 | 4.35 | | 5.42 | 6.35 | 2.9 | |
| **1c** | | 1.15 | 4.25 | | 5.45 | 6.22 | 7.85 | Cyclohexyl |
| **2c** | | 1.00 | 420 | 5.20 | 4.40 | | 8.2 | 1.5 (m, 11 H), cyclohexyl |
| **2d** | | 1.10 | 4.33 | 5.20 | 5.42 | | 7.6 | |
| **2g** | 1.5 | 1.12 | 4.40 | 5.50 | | | 8.0 | 2.0 (m, 11 H, |
| **2h** | 1.4 | 1.22 | 4.22 | | 5.35 | | 7.8 | |
| **2k** | | 1.20 | 4.30 | | 5.40 | | 7.6 | 1.8 (m, 11 H, cyclohexyl |
| **2l** | | 1.16 | 4.40 | | 5.52 | | 7.2 | |
| **3d** | 1.4 | 1.12 | 4.20 | | 5.50 | | 7.8 | 2.0 (m, 11 H, cyclohexyl |
| **3g** | | 1.23 | 4.40 | | 5.45 | | 7.6 | 1.8 (m, 11 H, cyclohexyl |
| **4a** | | 1.18 | 4.17 | 5.32 | 5.40 | 6.25 | 7.8 | |
| **4b** | 1.35 | 1.10 | 4.30 | | 5.52 | 6.30 | 7.9 | |
| **4c** | | 1.18 | 4.42 | | 5.35 | 6.23 | 7.6 | |
| **5b** | | 1.23 | 4.20 | 5.21 | 5.52 | | 7.9 (a) | |
| **5c** | | 1.18 | 4.40 | | 5.50 | | 7.6 (a) | |
| **6a** | | | | 5.20 | 5.45 | 6.25 | 7.56 | 10.7 (S, COOH) |
| **6b** | | | | | 5.35 | 6.40 | 7.6 | 10.8 (S, COOH) |
| **7a** | | | | | 5.40 | | 7.9 | 1.8 (S, COOH) |
| | | | | | | | | 10.6 (S, COOH) |
| **7b** | | | | | 5.32 | | 7.6 | 10.9 (S, COOH) |

R′ = H, R′ = $CH_3$, R′ = $C_6H_5$.
The NH protons are overlapped by the complex aromatic multiplet; s: singlet, t: triplet (J = 7.0 Hz), q: quartet (J = 7.0 Hz), d: doublet (J = 5.0 Hz) and m: multiplet.

Unicam SP 800 spectrophotometer. The $^1$H nmr spectra were recorded on a Varian T-60 and Jeol 100 spectrometers for solutions in deuteriochloroform with TMS as an internal standard.

1-(*p*-Sulfamylphenyl)-4-bromo-3-ethoxycaronyl-5-[δ-substituted-styryl]pyrazoles (**4**) (Tables II, III and IV).

A solution of **1** (0.1 mole) in chloroform (100 ml) was stirred with bromine (0.1 mole) for 1 hour. The product which separated (80% yield) during stirring was filtered off and crystallised from methanol in needles.

Substituted *p*-(3-Ethoxycarbonyl-5-[δ-substituted-styryl]-1-pyrazolyl)benzenesulfonylurea Derivatives (**2**) and Substituted *p*-(4-Bromo-3-ethoxycarbonyl-5-[α-substituted-styryl]-1-pyrazolyl)benzenesulfonylurea Derivatives (**5**) (Tables I, II, III and IV.)

A mixture of **1** or **4** (0.05 mole) and anhydrous potassium carbonate (0.1 mole) in dry acetone (100 ml) was refluxed with stirring for 15 hours. A solution of the appropriate isocyanate (0.075 mole) in dry acetone (20 ml) was added drop by drop at this temperature and refluxing was continued overnight. The acetone was distilled under reduced pressure and the solid residue was dissolved in water. The product (85% yield) was isolated after acidification with 2*N* hydrochloric acid and it was purified by recrystallization from ethanol in needles.

The 4-bromopyrazole ester **5** were also obtained after stirring a solution of **2** (0.1 mole) in chloroform (100 ml) with bromine (0.1 mole) for 2 hours (65% yield).

Substituted-*p*-(3-Ethoxycarbonyl-5-[α-substituted styryl]-1-pyrazolyl)benzenesulfonylthiourea Derivatives (**3**) (Tables I, III, and IV).

A mixture of the pyrazole esters (**1**) (0.05 mole) and anhydrous potassium carbonate (0.1 mole) in dry acetone (100 ml) was refluxed with the appropriate isocyanate (0.06 mole). After stirring and refluxing the mixture for 10 hours, acetone was removed under reduced pressure, and the solid mass thus obtained was dissolved in water and acidified with 2*N* hydrochloric acid. The product (70% yield) was purified by crystallization from dilute ethanol.

*p*-(3-Carboxy-5-[α-substituted-styryl]-1-pyrazolyl-benzenesulfonylphenylurea (**7**) (Tables II, III and IV).

A mixture of the sulfamylphenylpyrazolecarboxylic acids **6** (0.05 mole) and anhydrous potassium carbonate (0.1 mole) in dry acetone (100 ml) was refluxed with stirring with appropriate isocyanate for 18 hours. Acetone was then removed under reduced pressure and the solid residue was dissolved in water. The product (75% yield) was isolated by acidification with 2*N* hydrochloric acid and purified by crystallisation from ethanol.

Furthermore, the pyrazolecarboxylic acids **7** were also obtained (70% yield) when the appropriate ester **2** (1 g) was heated under reflux with alcoholic solution of 2*N* potassium hydroxide (30 ml) for 1 hour. After concentration, cooling and acidification with dilute hydrochloric acid the titled compound separated out.

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