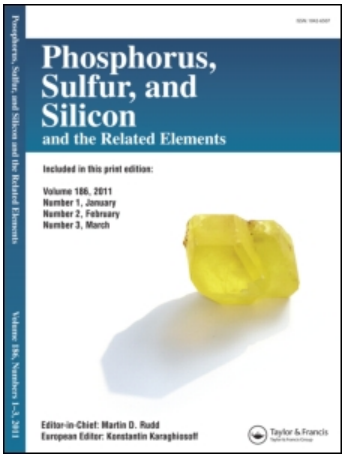

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Pyridazine Derivatives and Related Compounds Part 24.[1] Synthesis and Antimicrobial Activity of Some Sulfamoylpyrazolo[3,4-*c*]pyridazine Derivatives

Mona Hosny[a]; Fatma El-Mariah[a]; Ali Deeb[b]
[a] Department of Chemistry, Faculty of Girls, Ain Shams University, Cairo, Egypt [b] Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt

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Pyridazine Derivatives and Related Compounds Part 24.[1] Synthesis and Antimicrobial Activity of Some Sulfamoylpyrazolo[3,4-*c*]pyridazine Derivatives

Mona Hosny
Fatma El-Mariah
Department of Chemistry, Faculty of Girls, Ain Shams University, Cairo, Egypt

Ali Deeb
Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt

A series of new sulfamoylpyrazolo[3,4-c]pyridazine derivatives was synthesized. Some of these compounds show interesting antimicrobial activity.

Keywords 3-substituted sulfamoylpyrazolo[3,4-*c*]pyridazine; antimicrobial activity

INTRODUCTION

During the last years, we have been interested in the synthesis of substituted heterocycles containing the pyrazolo[3,4-*c*]pyridazine system with the aim of finding compounds with promising biological activities.[2–5]

On the other hand, the sulfonamides group forms the bioactive moiety of many compounds with therapeutical interest, such as antibacterials, diuretics, antidiabetics, and antibiotics.[6] In this article, we report the preparations and structural confirmations of 3-sulfamoylpyrazolo[3,4-*c*]pyridazine derivatives, and reported the antimicrobial activity of these compounds against some gram (positive) and gram (negative) bacteria, *Candida albicans*, and *Aspergillus niger*.

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Address correspondence to Ali Deeb, Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt. E-mail: dralideeb@hotmail.com

The precursor 3-diazo-4,5-diphenylpyrazolo[3,4-*c*]pyridazine **1** was synthesized following the literature procedure by diazotization of 3-amino-4,5-diphenyl-1*H*-pyrazolo[3,4-*c*]pyridazine with sodium nitrite in glacial acetic acid at room temperature.[7]

The thiation of 3-diazo derivative **1** using thiourea in absolute ethanol resulted in the formation of thiouronium derivative, which on hydrolysis with 2 N sodium hydroxide followed by acidification with hydrochloric acid (pH 2), gave 3-mercapto-4,5-diphenyl-1*H*-pyrazolo[3,4-*c*]pyridazine **2** in a 90% of yield. Compound **2** was used as a starting material in the synthesis of the target heterocycles. Thus when **2** was treated with chlorine gas in presence of 90% acetic acid at 0°C the corresponding sulfonyl chloride **3** was obtained.

Because of the instability of the sulfonyl chloride **3**, the crude product was usually converted directly to the more stable sulfonamides by amidation. In this manner, a number of new derivatives of sulfonamides have been prepared (Scheme 1). Treatment with aqueous ammonia yielded the sulfonamide, and the reaction with hydrazine hydrate gave the sulfonhydrazide derivatives **4a**,**b**, respectively, in good yields.

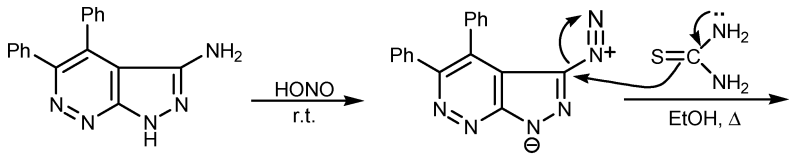
On the other hand, aliphatic amines such as methyl, n-propyl, i-butyl, and benzyl amines reacted with **3** in refluxing benzene to furnish the respective 3-alkanesulfamoyl-4,5-diphenyl-1*H*-pyrazolo[3,4-*c*]pyridazine **4c–f**. Likewise, reaction of sulfonyl chloride **3** with aromatic amines such as aniline, anthranilic acid, *p*-aminobenzic acid, *p*-anisidine, *p*-toluidine, *p*-chloroaniline, sulfanilic acid, and 1-naphthylamine resulted in the formation of 3-arenesulfamoyl derivatives **4g–n**.

It was of considerable interest to study the reaction of compound **3** with glycine as a possible new route to design a tricyclic compound containing a thiadiazine-1,1-dioxide ring. The reaction was carried out in boiling benzene afforded 3-carboxymethylsulfamoyl derivative $\mathbf{4}_o$. An attempt to cyclize the acid $\mathbf{4}_o$ was unsuccessful. Further attempts to carry out the cyclization under modified conditions, and on extension of the synthetic scope of these reactions are under study.

The structural formulas of all newly synthesized compounds were confirmed by elemental and spectroscopic analyses (c.f., Experimental section).

Screening for Antimicrobial Activities

Applying the agar plate diffusion technique,[8] the newly synthesized compounds were screened in vitro for antimicrobial activity against representative of gram positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*), gram negative bacteria (*Escherichia coli* and *Pseudomonas*



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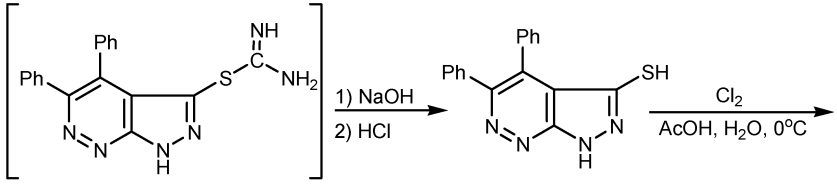

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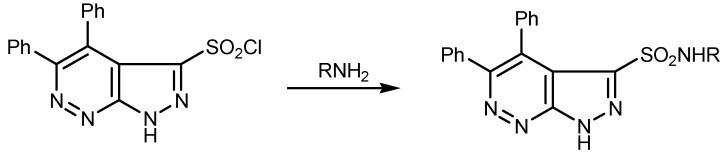

3 **4a-o**

a, R = H
b, R = NH_2
c, R = Me
d, R = *n*-Pr
e, R = *i*-Bu
f, R = Bn
g, R = Ph
h, R = $C_6H_4CO_2H$(*o*)
i, R = $C_6H_4CO_2H$ (*p*-)
j, R = C_6H_4OMe (*p*-)
k, R = C_6H_4Me (*p*-)
l, R = C_6H_4Cl (*p*-)
m, R = $C_6H_4SO_3H$ (*p*-)
n, R = 1-naphthyl
o, R = CH_2CO_2H

SCHEME 1

aeruginosa), yeast (*Candida albicans*), and fungi (*Asperggillus niger*). In this method, a standard 5 mm diameter sterilized filter paper disc impregnated with the compound (0.3 mg/0.1 mL of dimethylformamide) was placed on an agar plate seeded with the test organism. The plates were incubated for 24 h at 37°C. The zone of inhibition of bacterial growth around the disc was observed. The screening results given in Table 1 indicated that all the compounds exhibited antimicrobial activity against all the test organisms.

TABLE I Antibacterial and Antifungal Activity

No.	*Bacillus subtitils*	*Staph. Aureus*	*Esch. Coli*	*Pseud. aeurgin*	*Candida albicans*	*Asp. Niger*
2	+++	+++	++	++	++	−
3	+++	+++	++	++	++	−
4a	+++	++	−	−	−	++
4b	++	+++	++	+	++	++
4c	+++	+++	++	++	++	++
4d	+++	+++	++	++	++	++
4e	+++	+++	++	++	++	++
4f	++	+++	++	++	++	++
4g	+++	+++	−	−	++	++
4h	++	+++	−	−	++	++
4i	++	+++	++	++	++	−
4j	++	+++	++	++	++	++
4k	+++	+++	++	++	++	++
4l	+++	+++	++	++	++	−
4m	+++	+++	++	++	++	++
4n	+++	+++	++	++	++	++
4o	+++	+++	++	++	++	++
Cipr	+++	+++	+++	+++	−	−
Nys	−	−	−	−	+++	−

Zone of inhibition : ++ = 15–20 mm; +++ = 25–30 mm; − = negative inhibition.

Most of the synthesized compounds showed a remarkable activity against gram positive bacteria and less active against gram negative, as well as yeast and fungi.

From these results, we can conclude that the biologically active compounds are nearly as active as standard antibiotic Ciprofloxacin and less active than the fungicide, Nystin.

EXPERIMENTAL

Melting points were determined in open glass capillaries and are uncorrected. The IR spectra of the compounds were recorded on a Perkin-Elmer spectrophotometer model 1430 as potassium bromide pellets. The mass spectra were recorded on a mass spectrometer HP model MS 5988 E1 70 ev. Reactions were routinely followed by thin layer chromatography (tlc) on silica gel F_{254} aluminum sheets (Merck). The spots were detected by uv irradiation at 254–365 nm.

Compound **1** was synthesized as reported previously.[7]

2-Mercapto-4,5-diphenyl-1*H*-pyrazolo[3,4-*c*]pyridazine 2

To a solution of 3-diazo-4,5-diphenylpyrazolo[3,4-*c*]pyridazine **1** (1.0 g, 3.35 mmoles) in ethanol (20 mL), thiourea (0.3 g, 3.44 mmoles) was

added. The reaction mixture was refluxed for 3 h. The solvent was evaporated under reduced pressure, and the residue was treated with 2N sodium hydroxide (20 mL). The mixture was refluxed for 15 min, filtered on hot, and the cooled filtrate was treated with 3N hydrochloric acid (pH = 6). The precipitate was filtered off, washed with water, dried, and recrystallized from ethanol to give **2**, yield 0.9 g (88.2%), m.p. 260–261°C; IR: 3150 (NH), 3059 ($CH_{arom.}$), 2400 (SH), 1620 (C=N) cm^{-1}; MS, *m/z* (%): 305 (M^+ + 1, 29), 304 (M^+, 55), 303 (M^+ - H, 100), 271 (M^+ - SH, 21, ion A), 245 (M^+ - C(=N)SH, 10). Anal. Calcd. for $C_{17}H_{12}N_4S$: C, 67.08; H, 3.98; N, 18.41. Found: C, 66.80; H, 3.80; N, 18.20.

4,5-Diphenyl-1*H*-pyrazolo[3,4-*c*]pyridazine-3-sulfonylchloride 3

In a solution of 3-mercapto, derivative **2** (1.0 g, 3.28 mmoles) in acetic acid (9 mL) and water (1 mL), chlorine gas was bubbled at 0°C. After 1 h, the precipitate was filtered, washed with water several times, and dried to give 3-sulfonylchloride derivative **3**, 0.9 g (74.4%).

4,5-Diphenyl-1*H*-pyrazolo[3,4-*c*]pyridazine-3-sulfonamide 4a

The sulfonylchloride **3** (1.0 g, 2.69 mmoles) was added to conc. ammonium hydroxide (20 mL). The reaction mixture was heated on a steam bath for 4 h; the volume was reduced to its half and neutralized with 6 N HCl to give a solid product. The solid product was filtered, washed with water, dried, and recrystallized from ethanol to give **4a**, yield 0.9 g (94.7%), m.p. 265–266°C; IR: 3249 (NH_2), 3150 (NH), 3055 ($CH_{arom.}$), 1302, 1163 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 14.5 (s, 1H, NH), 7.5 (s, 2H, NH_2) and 7.3 (s, 10H, 2Ph); MS, *m/z* (%): 351 ($M^{+\cdot}$ 1.4), 271 (M^+ -SO_2NH_2, 12.8). Anal. Calcd. for $C_{17}H_{13}N_5O_2S$: C, 58.11; H, 3.73; N, 19.93. Found: C, 57.80; H, 3.60; N, 19.80.

4,5-Diphenyl-1*H*-pyrazolo[3,4-*c*]pyridazine-3-sulfohydrazide 4b

To a solution of sulfonylchloride **3** (1.0 g, 2.69 mmoles) in benzene (20 mL), hydrazine hydrate (0.5 mL, 80%) was added. The reaction mixture was heated under reflux for 3 h. The solvent was evaporated under reduced pressure. The residue was triturated with water, filtered, dried, and recrystallized from ethanol to give **4b**, yield 0.95 g (96.1%), m.p. 260–261°C; IR: 3400 (br, NH_2), 3149 (NH), 3056 ($CH_{arom.}$), 1303, 1163 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 14.95 (s, 1H, pyrazole NH), 8.4 (s, 1H, $\underline{N}HNH_2$), 7.2–7.3 (m, 10H, 2Ph), 4.1 (br s, 2H, NH_2); MS *m/z* (%):

368 (M^++ 2, 2.2), 367 (M^++ 1, 1.8), 271 (M^+ - SO_2NHNH_2, 63). Anal. Calcd. for $C_{17}H_{14}N_6O_2S$: C, 55.72; H, 3.85; N, 22.94. Found: C, 55.50; H, 3.60; N, 22.70.

3-Substituted sulfamoyl-4,5-diphenyl-1*H*-pyrazolo-[3,4-*c*]pyridazines 4c-o

General Procedure

To a solution of sulfonylchloride derivative **3** (1.0 g, 2.69 mmoles) in benzene (20 mL), substituted amines (3.0 mmoles) was added. The reaction mixture was heated under reflux for 3 h. The solvent was concentrated. The solid product was collected and recrystallized from ethanol.

4c (R = Me): Mp 240–241°C; yield 96.9%; 3250, 3141 (NH groups), IR: 3055 ($CH_{arom.}$), 2967 ($CH_{aliph.}$), 1653 (C=N), 1302, 1163 (SO_2); MS *m/z* (%): 365 (M^+, 1.5), 271 (M^+ - SO_2NHCH_3, 69). Anal. Calcd. for $C_{18}H_{15}N_5O_2S$: C, 59.16; H, 4.14; N, 19.17. Found: C, 58.90; H, 4.00; N, 18.90.

4d (R = n-Pr): Mp 260–261°C; yield 84.9%; IR: 3300, 3139 (NH groups), 3056 ($CH_{arom.}$), 2941 ($CH_{aliph.}$), 1640 (C=N), 1303, 1164 (SO_2) cm^{-1}. MS *m/z* (%): 393 (M^+, 0.08), 350 (M^+ - $CH_2CH_2CH_3$, 0.09), 335 (M^+- NHPr, 0.08), 271 (M^+ - SO_2NHPr, 7.8). Anal. Calcd. for $C_{20}H_{19}N_5O_2S$: C, 61.05; H, 4.87; N, 17.80. Found: C, 60.80; H, 4.60; N, 17.50.

4e (R = i-Bu): Mp 195-196°C; yield 77.98%; IR: 3200, 3150 (NH groups), 3058 ($CH_{arom.}$), 2961 ($CH_{aliph.}$), 1679 (C=N), 1313, 1166 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 14.9 (s, 1H, pyrazol-NH), 7.6 (s, 1H, NH), 7.4–7.3 (m, 10H, 2Ph), 2.7 (t, 2H, CH_2), 1.9–1.7 (m, 1H, CH), 0.9 (d, 6H, $2CH_3$). Anal. Calcd. for $C_{21}H_{21}N_5O_2S$: C, 61.89; H, 5.19; N, 17.19. Found: C, 61.70; H, 5.00; N, 16.90.

4f (R = Bn): Mp 204–205°C, yield 67.2%; IR: 3200, 3100 (NH groups), 3058 ($CH_{arom.}$), 2966 ($CH_{aliph.}$), 1640 (C=N), 1356, 1162 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 15 (s, 1H, pyrazol NH), 7.4 (s, 1H, NH), 7.3–7.2 (m, 15H, 3Ph), 3.4 (d, 2H, CH_2); MS *m/z* (%): 441 (M^+, 8), 335 (M^+- $PhCH_2NH$), 271 (M^+ - $PhCH_2NHSO_2$, 40), 91 ($PhCH_2$, 100). Anal. Calcd. for $C_{24}H_{19}N_5O_2S$: C, 65.29; H, 4.34; N, 15.86. Found: C, 65.00; H, 4.10; N, 15.60.

4g (R = Ph): MP 115–116°C, yield 82.6%; IR : 3500 (NH), 3110 (NH), 3054 ($CH_{arom.}$), 1627 (C=N), 1360, 1162 (SO_2); ^{1}H-NMR (DMSO-d_6): δ 7.4–7.1 (m, 15m, 3Ph), 6.8 (d, 1H, NH); MS *m/z* (%): 427 (M^+, 9.9), 271 (M^+ - $PhNHSO_2$, 12). Anal. Calcd. for $C_{23}H_{17}N_5O_2S$: C, 64.62; H, 4.01; N, 16.38. Found: C, 64.40; H, 3.90; N, 16.10.

4h (R = $C_6H_4CO_2H$ (*o*-)): Mp 210–211°C, yield 66.9%; IR: 3422 (OH), 3200, 3158 (NH groups), 3059 ($CH_{arom.}$), 1652 (C=N), 1368, 1120 (SO_2);

MS *m/z* (%): 475 (M^+ - 4, 10), 354 (M^+ - C_6H_4COOH, 1.9). Anal. Calcd. for $C_{24}H_{17}N_5O_4S$: C, 61.13; H, 3.63; N, 14.85. Found: C, 60.90; H, 3.50; N, 14.70.

4i (R = $C_6H_4CO_2H$ (*p*-)): Mp 240–241°C; yield 74.8%; IR: 3500 (OH), 3200, 3150 (NH groups), 3056 ($CH_{arom.}$), 1702 (C=O), 1606 (C=N), 1337, 1165 (SO_2); MS *m/z* (%): 471 (M^+, 0.4), 334 (M^+ - NHC_6H_4COOH, 0.4). Anal. Calcd. for $C_{24}H_{17}N_5O_4S$: C, 61.13; H, 3.63; N, 14.85. Found: C, 61.00; H, 3.50; N, 14.60.

4j (R = C_6H_4OMe (*p*-)): Mp 200–201°C, yield 77.23%; IR: 3210, 3150 (NH groups), 3056 ($CH_{arom.}$), 2838 ($CH_{aliph.}$), 1509 (OCH_3), 1361, 1121 (SO_2); ^1H NMR (DMSO-d_6): δ 14.9 (s, 1H, pyrazol–NH), 6.79 (s, 1H, NH), 7.40–7.14 (m, 14H, phenyl protons), 2.51 (s, 3H, OCH_3); MS *m/z* (%): 457 (M^+, 1.5), 427 [M^++ 1 – OCH_3, 0.2 (ion A)], 350 [ion A–C_6H_4, 0.5 (ion B)], 336 [ion B–NH, 0.2 (ion C)], 305 [ion C–O_2, 100 (ion D)], 271 [ion D – S, 22.9]. Anal. Calcd. for $C_{24}H_{19}N_5O_3S$: C, 63.00; H, 4.18; N, 15.31. Found: C, 62.80; H, 4.00; N, 15.00.

4k (R = C_6H_4Me (*p*-)), Mp 210–211°C, yield 75.6%; IR: 3300, 3150 (NH groups), 3056 ($CH_{arom.}$), 2919 ($CH_{aliph.}$), 1620 (C=N), 1361, 1164 (SO_2). Anal. Calcd. for $C_{24}H_{19}N_5O_2S$: C, 65.29; H, 4.34; N, 15.86. Found: C, 65.00; H, 4.10; N, 15.60.

4l (R = C_6H_4Cl (*p*-)), Mp 180–181°C, yield 68.5%; IR: 3300, 3100 (NH groups), 3056 ($CH_{arom.}$), 2967 ($CH_{aliph.}$), 1621 (C=N), 1303, 1162 (SO_2); ^1H NMR (DMSO-d_6): δ 14.6 (s, 1H, pyrazol NH), 7.4–7.3 (m, 14H, phenyl protons), 7.1 (s, 1H, NH); MS *m/z* (%): 461 (M^+, 0.58), 349 (M^+ - C_6H_4Cl, 0.2), 335 (M^+ - NHC_6H_4Cl, 0.37), 271 (M^+ - $SO_2NHC_6H_4Cl$, 28). Anal. Calcd. for $C_{23}H_{16}ClN_5O_2S$: C, 59.80; H, 3.49; N, 15.16. Found: C, 59.60; H, 3.20; N, 15.00.

4m (R = $C_6H_4SO_3H$ (*p*-)): Mp 210–211°C, yield 73.1%; IR: 3400, 3147 (NH groups), 3058 ($CH_{arom.}$), 1654 (C=N), 1366, 1120 (SO_2); ^1H NMR (DMSO-d_6): δ 14.97 (s, 1H, pyrazol NH), 7.6–7.2 (m, 14H, phenyl protons), 6.4 (br s, 1H, NH); MS *m/z* (%): 409 (M^++ 2, 0.07), 507 (M^+, 0.06), 350 (M^+ - $HO_3SC_6H_4$, 0.18), 335 (M^+ - $HO_3SC_6H_4NH$, 0.15), 303 (M^+ - $HO_3SC_6H_4NHO_2$, 0.21), 271 (M^+ - $HO_3SC_6H_4NHSO_2$, 100). Anal. Calcd. for $C_{23}H_{17}N_5O_5S_2$: C, 54.43; H, 3.38; N, 13.80. Found: C, 54.20; H, 3.10; N, 13.60.

4n (R = 1-Naphthyl), Mp 198–199°C, yield 62.2%; IR: 3400, 3200 (NH groups), 3056 ($CH_{arom.}$), 1363, 1162 (SO_2); MS *m/z* (%): 478 (M^++ 1, 0.59), 477 (M^+, 1.37), 350 (M^+ - naphthyl, 1.46), 335 (M^+ - HN-naphthyl, 0.5), 271 (M^+ - SO_2NH-naphthyl, 87.8). Anal. Calcd. for $C_{27}H_{19}N_5O_2S$: C, 67.91; H, 4.01; N, 14.67. Found: C, 67.70; H, 3.90; N, 14.40.

4o (R = CH_2COOH), Mp 220–221°C, yield 67.6%; IR: 3400, 3100 (NH groups), 3057 ($CH_{arom.}$), 2921 ($CH_{aliph.}$), 1655 (C=O), 1366, 1118 (SO_2); MS *m/z* (%): 409 (M^+, 0.05), 350 (M^+- CH_2COOH, 0.13), 335

(M^+- $HNCH_2COOH$, 0.17), 271 (M^+- SO_2HNCH_2COOH, 46.3), 270 (M^+- SO_2HNCH_2COOH, H, 100). Anal. Calcd. for $C_{19}H_{15}N_5O_4S$: C, 55.74; H, 3.69; N, 17.11. Found: C, 55.50; H, 3.40; N, 17.00.

REFERENCES

[1] Part 23: A. Deeb, F. Yasine, N. Auef, and W. Shehta, *Dyes & Pigments*, in press.
[2] A. Deeb and M. Kotb, *Heterocycles*, **63,** 1143 (2004).
[3] A. Deeb, F. El-Mariah, and M. Hosny, *Bioorg. Med. Chem. Lett.*, **14,** 15013 (2004).
[4] A. Amer, M. Zayed, A. Deeb, and A. Ali, *J. Chem. Res.*, 643 (2005).
[5] F. El-Mariah, M. Hosny, and A. Deeb, *Phosphorus, Sulfur, and Silicon*, **181,** 809 (2006).
[6] (a) Lednicer and L. A. Mitscher, *The Organic Chemistry of Drug Synthesis*, (Wiley, New York, 1977), Vol. **1**, pp. 120; (b) Lednicer and L. A. Mitscher, *The Organic Chemistry of Drug Synthesis*, (Wiley, New York, 1980), Vol. 2, pp. 112; (c) Lednicer and L. A. Mitscher, *The Organic Chemistry of Drug Synthesis* (Wiley, New York, 1984), Vol. 3, pp. 61.
[7] A. Deeb, B. Bayoumy, A. Hataba, and R. Fikry, *Heterocycles*, **32,** 901 (1991).
[8] A. W. Bauer, W. W. Mkriby, J. C. Scherris, and M. Turck, *Am. J. Clin. Pathol.* **45,** 493 (1966).