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Heterocycles from Pyrazoloylhydroximoyl Chloride: Synthesis of Certain Quinoxaline, Benzothiadiazine, Benzoxadiazine, Quinazolinone, Imidazo[1,2-*a*]pyridine, Imidazo[1,2-*a*]pyrimidine, Isoxazole, Pyrazolo[3,4-*d*]pyridazine and Pyrrolidino[3,4-*d*]isoxazolin-4,6-dione Derivatives

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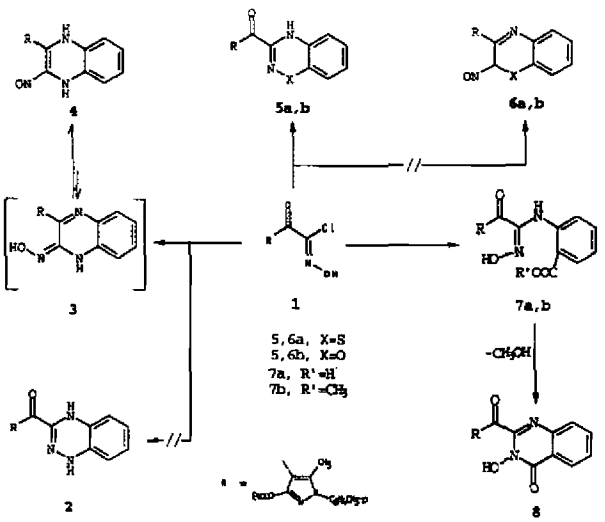
3-Ethoxycarbonyl-5-methyl-1-(4-methylphenyl)-4-pyrazoloylhydroximoyl chloride (**1**) reacted with *o*-phenylenediamine, *o*-aminothiophenol, *o*-aminophenol and methyl anthranilate to afford 3-nitrosoquinoxaline, benzothiadiazine, benzoxadiazine, and 3-hydroxyquinazoline, respectively. Imidazo[1,2-*a*]pyridine, imidazo[1,2-*a*]pyrimidine and isoxazole derivatives were obtained *via* the reaction of **1** with 2-aminopyridine, 2-aminopyrimidine and the appropriate active methylene compounds, respectively. Pyrazolo[3,4-*d*]pyridazines, and pyrrolidino[3,4-*d*]isoxazolines derivatives were also synthesized. The structures of the newly synthesized compounds were established on the basis of spectral data and alternate synthesis whenever possible.

Pyrazoles have been reported to have different biological activities, e.g. analgesic, antipyratic, antiinflamatory and antibacterial properties.[1-4] Imidazo[1,2-*a*]pyrimidines have been reported to posses analgesic, antiinflamatory and antiviral properties.[5-7] Also, several isoxazole derivatives have been investigated for therapeutic uses, especially as tranquilizing agents and CNS regulants.[8] In conjunction with our previous work,[9-15] we report herein the synthesis and utilization of pyrazoloylhydroximoyl chloride **1** in heterocyclic synthesis for biological evaluation.

RESULTS AND DISCUSSION

Treatment of hydroximoyl chloride **1** with *o*-phenylenediamine, in ethanol at room temperature, gave a single product as evidenced by TLC. This product could be 1,2,4-benzotriazine **2** or quinoxaline **3** as depicted in Scheme I. The IR (cm^{-1}) spectrum of the product exhibits absorption bands at 3381 (NH), 1712 (CO ester) and a nitroso absorption at 1570. Thus, the product was assigned the structure of 2-[3-ethoxycarbonyl-5-methyl-1-(4-methylphenyl)pyrazol-4-oyl]-4H-3-oximoquinoxaline (**3**). Compound **3** exists in the isomeric structure **4**. Similarly, the reaction of **1** with each of 2-aminothiophenol and 2-aminophenol, in ethanol at room temperature, afforded benzothiadiazine **5a** and benzoxadiazine **5b**, respectively (*cf.* Scheme I). The isomeric structure **6** was readily ruled out on the basis of elemental and spectral data. Thus, the IR (cm^{-1}) spectrum of **5a**, for example, showed absorption bands at 1728 and 1691 due to the two carbonyl groups. Its ^1H NMR (δ ppm) spectrum revealed signals at 1.18 (s, 3H, $\underline{CH_3}CH_2$), 2.31 (s, 3H, CH_3-*p*), 2.41 (s, 3H, pyrazole C_5-CH_3), 4.23 (q, 2H, $CH_3\underline{CH_2}$) and 7.25-7.69 (m, 9H, ArH's and NH).

Scheme I

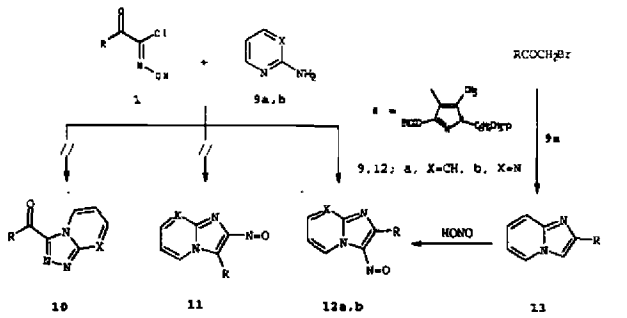


When **1** was treated with anthranilic acid or its methyl ester, in ethanol, it gave compounds **7a,b**, respectively. The structure of these products were in agreement with both elemental and spectral data. Thus the IR (cm^{-1}) spectrum of **7a** showed bands at 3400-2800 (OH and NH), 1733, 1720 (CO ester and acid), and 1664 (CO conjugated); and for com-

pound **7b** showed bands at 3335 (NH), 1732 (CO ester) and 1688 (CO). ^{1}H NMR (δ ppm) spectrum for compound **7a** showed signals at 1.04 (t, 3H, $\underline{CH_3}CH_2$), 2.52 (s, 6H, $C_6H_4\underline{CH_3}$-*p* and pyrazole C_5-CH_3), 4.09 (q, 2H, $CH_3\underline{CH_2}$), 6.65-7.81 (m, 9H, ArH's and NH), 10.04 (s, 1H, NO$\underline{H}$) and at 10.95 (s, 1H, CO$\underline{OH}$). ^{1}H NMR (δ ppm) spectrum for compound **7b** showed signals at 1.25 (t, 3H, $\underline{CH_3}CH_2$), 2.41 (s, 3H, $C_6H_4\underline{CH_3}$-*p*), 2.44 (s, 3H, pyrazole C_5-CH_3), 3.89 (s, 3H, $\underline{CH_3}OCO$), 4.21 (q, 2H, $CH_3\underline{CH_2}$), 6.91-7.99 (m, 8H, ArH's), 8.43 (s, br, 1H, NH) and at 10.12 (s, 1H, NO$\underline{H}$). Compound **7b** was converted to 2-[3-ethoxycarbonyl-5-methyl-1-(4-methylphenyl)pyrazol-4-oyl]-3-hydroxy-4-(3H)-quinazolinone **8** *via* loss of one molecule of methanol, by boiling in xylene.

On the other hand, treatment of **1** *with two equivalents* of 2-aminopyridine (**9a**), in ethanol at room temperature, gave a single product in a quantitative yield, which was assigned as 2-[3-ethoxycarbonyl-5-methyl-1-(4-methylphenyl)pyrazol-4-yl]-3-nitrosoimidazo[1,2-*a*]pyridine (**12a**) (*cf.* Scheme II). The triazolopyridine structure **10** was readily ruled out since nitroso absorption, in the region 1580 cm^{-1}, was observed in the IR spectrum of the product. Structure **11** was also rejected because the reaction of 2-aminopyridine with α-haloketones was reported to yield 2-substituted imidazo[1,2-*a*]pyridine rather than the corresponding 3-substituted analogs.[16] Furthermore, nitrosation of 2-pyrazolylimidazo[1,2-*a*] pyridine **13**, with sodium nitrite in acetic acid, gave a product identical in all aspects with **12a**.

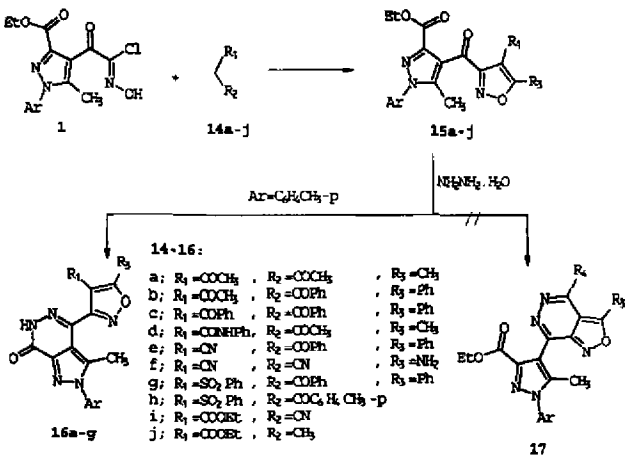
Scheme II



Similarly, the reaction of **1** with two equivalents of 2-aminopyrimidine (**9b**), in ethanol at room temperature, produced 2-[3-ethoxycarbonyl-5-methyl-1-(4-methylphenyl)-pyrazol-4-yl]-3-nitrosoimidazo[1,2-*a*]pyrimidine (**12b**) in a quantitative yield. Structure **12** was in agreement with both elemental and spectral data.

The reaction of hydroximoyl halides with doubly activated methylene compounds provides a regiospecific synthesis of isoxazole derivatives containing a wide variety of alkyl or aryl substituents in the 5-position.[17] Thus, the addition of compound **1** to acetylacetone (**14a**), in ethanolic sodium ethoxide solution at room temperature, yielded 4-acetyl-5-methyl-3-[3-ethoxycarbonyl-5-methyl-1-(4-methylphenyl)-4-oyl]isoxazole (**15a**). The structure of **15a** was established on the basis of its elemental analysis and spectral data. Thus its ^{1}H NMR (δ ppm) spectrum showed signals at 1.25 (t, 3H, $\underline{CH_3}CH_2$); 2.42 (s, 3H, $C_6H_4\underline{CH_3}$-*p*); 2.49 (s, 3H, pyrazole C_5-CH_3); 2.52 (s, 3H, isoxazole C_5-CH_3); 2.70 (s, 3H, CH_3CO); 4.23 (q, 2H, $CH_3\underline{CH_2}$), and 7.33 (m, 4H, ArH's). The IR (cm^{-1}) spectrum revealed bands at 1751, 1690 and 1665 due to ester, acetyl and pyrazoloyl carbonyls, respectively. Similarly, compound **1** reacted with each of benzoylacetone, dibenzoylmethane, acetoacetanilide, benzoylacetonitrile, malononitrile, β-ketosulfones, ethyl cyanoacetate and ethyl acetoacetate (**14b-j**), in ethanolic sodium ethoxide solution at room temperature, to give the isoxazole derivatives **15b-j**, respectively (*cf.* Scheme III). Evidence for the assigned structures were provided *via* their elemental and spectral data. Thus the IR (cm^{-1}) spectrum of **15f** showed absorption bands at 3345, 3270 (NH_2), 2231 (CN), 1725 (CO ester) and 1667 (CO). Its ^{1}H NMR (δ ppm) spectrum revealed signals at 1.35 (t, 3H, $\underline{CH_3}CH_2$); 2.42 (s, 3H, $C_6H_4\underline{CH_3}$-*p*); 2.49 (s, 3H, pyrazole C_5-CH_3); 4.42 (q, 2H, $CH_3\underline{CH_2}$); 5.60 (s, br, 2H, NH_2) and 7.3-7.6 (m, 4H, ArH's).

Scheme III

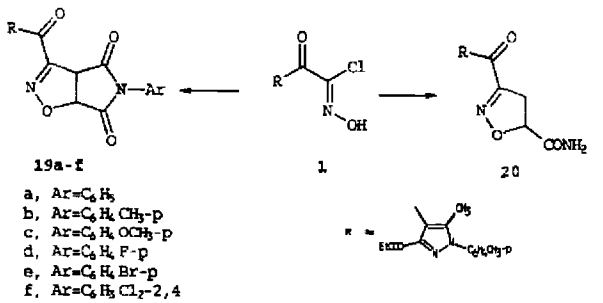


The reaction of isoxazoles **15a-g** with hydrazine hydrate in refluxing ethanol, afforded the corresponding 2*H*-pyrazolo[3,4-*d*]pyridazine derivatives **16a-g**, respectively. The structure of the products was elucidated by their elemental and spectral data. The characteristic ethoxycarbonyl signals were absent in the ^{1}H NMR spectra of **16a-g**. Structure **17** was readily ruled out on the basis of spectral studies

and elemental analysis data.

The reaction of **1** with some dipolarophiles such as *N*-arylmaleimides and acrylamide was studied. Thus, treatment of **1** with various *N*-arylmaleimides **18a-f** in boiling toluene afforded 5-aryl-3-[3-ethoxycarbonyl-5-methyl-1-(4-methylphenyl)pyrazol-4-oyl]pyrrolidino[3,4-d]isoxazoline-4,6-diones **19a-f** (*cf.* Scheme IV). Structure **19** was established on the basis of elemental analyses and spectral data. For example, the ^{1}H NMR (δ ppm) spectrum of **19a** showed signals at 1.30 (t, 3H, $\underline{CH_3}CH_2$); 2.42 (s, 3H, $C_6H_4CH_3$-*p*); 2.45 (s, 3H, pyrazole C_5-CH_3); 4.47 (q, 2H, $CH_3\underline{CH_2}$); 5.12 (d, 1H, isoxazoline H-4), 5.69 (d, 1H, isoxazoline H-5) and 7.10-7.40 (m, 9H, ArH's). The IR spectra of **19** showed absorption bands at 1790-1640 cm^{-1}, attributed to the presence of (-CO-NR-CO-) grouping and ester and conjugated carbonyls.

Scheme IV



Similarly, the reaction of **1** with acrylamide, in boiling toluene, afforded 5-carboxamido-3-[3-ethoxycarbonyl-5-methyl-1-(4-methylphenyl)pyrazol-4-oyl]-Δ^2-isoxazoline-(**20**). Elemental and spectral data were consistent with the assigned structure. The ^{1}H NMR (δ ppm) spectrum of **20** revealed signals at 1.33 (t, 3H, $\underline{CH_3}CH_2$); 2.40 (s, 3H, $C_6H_4\underline{CH_3}$-*p*); 2.56 (s, 3H, pyrazole C_5-CH_3); 3.66 (d, 2H, isoxazoline H-4); 4.31 (q, 2H, $CH_3\underline{CH_2}$); 5.16 (t, 1H, isoxazoline H-5); 6.2 (s, br, 2H, NH_2) and 7.1-7.4 (m, 4H, ArH's). Its IR spectrum (cm^{-1}) exhibits bands at 3371-3190, 1735, and 1685 due to the amino and carbonyl groups.

EXPERIMENTAL SECTION

M.p.s were determined on an Electrothermal melting point apparatus. IR spectra were recorded (KBr) on a Shimadzu FT-IR 8201 PC spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer and chemical shifts were expressed in δ (ppm) units using TMS as internal reference. Elemental analyses were carried out at the Microanalytical Center at Cairo University. 4-Acetyl-3-ethoxycarbonyl-1-(4-methylphenyl)-5-methylpyrazole[18] and 4-bromoacetyl-3-ethoxycarbonyl-5-methy-1-(4-methylphenyl)pyrazole[19] were prepared as described in the litrature.

3-Ethoxycarbonyl-5-methyl-1-(4-methylphenyl)pyrazolo-4-oyl Hydroximoyl Chloride (1)

To a solution of 1-[3-ethoxycarbonyl-5-methyl-1-(4-methylphenyl)pyrazoloyl-4-yl]ethane-1-one-dimethylsulfonium bromide (17.1 g, 40 mmol), sodium nitrite (3.5 g, 50 mmol) in water (50 mL) and dioxane (50 mL); 100 mL conc. HCl was added with stirring over a period of 1 h at room temperature. Stirring was continued for 2 h to produce a pale yellow solid which was collected by filtration and crystallized from benzene to give **1**.

Synthesis of 4, 5a,b, and 7a,b

A mixture of **1** (1.7 g, 5 mmol) and the appropriate bifunctional compounds (*o*-phynelendiamine, *o*-aminothiophenol, *o*-aminophenol, anthranilic acid or methyl anthranilate) (5 mmol each) in ethanol (20 mL) was stirred for 2 h and left overnight at room temperature. The resulting solid (or precipitated by dilution with water) was collected, washed with water and crystallized from ethanol to give **4**, **5a,b** and **7a,b**, respectively.

Synthesis of the Quinazolinone Derivative 8

A solution of **7b** (1 g) in dry xylene (15 mL) was heated under reflux for 2 h. The resulting precipitate, after cooling, was collected and crystallized from benzene to give **8**.

3-Nitrosoimidazo[1,2-*a*]pyridine and 3-Nitrosoimidazo-[1,2-*a*]pyrimidine, 12a,b

Method A

A mixture of **1** (1.7 g, 5 mmol) and 2-aminopyridine or 2-aminopyrimidine (5 mmol each) in ethanol (20 mL) was stirred for 2 h at room temperature. The green solid was collected and crystallized from ethanol to give **12a,b**, respectively.

Method B

A mixture of **13** (1 g) in acetic acid (15 mL) was cooled to 0-5 °C. Then saturated sodium nitrite solution (15 mL) was added dropwise while stirring. The green solid was collected and crystallized from ethanol to give a compound identical in all aspects to **12a** obtained above.

Table 1. Physical and Analytical Data of the Products

Compd. No.	mp/°C Yield/%	Molec. formula Molar mass/g	Analysis % Calcd./Found C	H	N
1	171-73	$C_{16}H_{16}ClN_3O_4$	54.94	4.61	12.01
	70	(349.77)	54.60	4.50	11.90
4	280-83	$C_{22}H_{21}N_5O_3$	65.50	5.24	17.35
	72	(403.41)	65.30	5.10	17.20
5a	230-32	$C_{22}H_{20}N_4O_3S$	62.84	4.80	13.32
	62	(420.49)	62.50	4.60	13.10
5b	127-30	$C_{22}H_{20}N_4O_4$	65.34	4.99	13.85
	85	(404.43)	65.00	4.60	13.60
7a	208-10	$C_{23}H_{22}N_4O_6$	61.33	4.92	12.44
	62	(450.45)	61.00	4.80	12.30
7b	200-202	$C_{24}H_{24}N_4O_6$	62.06	5.21	12.06
	70	(464.48)	62.10	5.10	11.90
8	158-59	$C_{23}H_{20}N_4O_5$	63.88	4.66	12.96
	65	(432.44)	63.70	4.60	13.10
12a	175-77	$C_{21}H_{19}N_5O_3$	64.77	4.92	17.99
	96	(389.42)	64.50	5.10	17.80
12b	228-230	$C_{20}H_{18}N_6O_3$	61.53	4.65	21.53
	92	(390.40)	61.70	4.80	21.70
13	128-30	$C_{21}H_{20}N_4O_2$	69.98	5.59	15.55
	60	(360.42)	69.80	5.30	15.10
15a	128-30	$C_{21}H_{21}N_3O_5$	63.79	5.36	10.63
	87	(395.42)	63.50	5.20	10.40
15b	144-46	$C_{26}H_{23}N_3O_5$	68.26	5.07	9.16
	83	(457.49)	68.20	5.10	9.00
15c	146-47	$C_{31}H_{25}N_3O_5$	71.67	4.85	8.09
	78	(519.56)	71.40	4.80	8.20
15d	175-76	$C_{26}H_{24}N_4O_5$	66.09	5.12	11.86
	80	(472.50)	65.80	5.00	11.60
15e	157-60	$C_{25}H_{20}N_4O_4$	68.17	4.58	12.72
	65	(440.46)	68.00	4.60	12.70
15f	190-92	$C_{19}H_{17}N_5O_4$	60.15	4.52	18.46
	72	(379.38)	59.90	4.50	18.30
15g	158-60	$C_{30}H_{25}N_3O_6S$	64.85	4.54	7.56
	86	(555.60)	64.70	4.60	7.40
15h	130-31	$C_{31}H_{27}N_3O_6S$	65.37	4.79	7.38
	81	(569.63)	65.30	4.60	7.30
15i	170-71	$C_{21}H_{22}N_4O_6$	59.15	5.20	13.14
	67	(426.42)	59.00	5.20	13.00
15j	170-73	$C_{22}H_{23}N_3O_6$	62.11	5.45	9.88
	60	(425.44)	62.00	5.30	9.80
16a	265-66	$C_{19}H_{17}N_5O_3$	62.80	4.72	19.28
	74	(363.37)	62.50	4.60	19.10
16b	242-45	$C_{25}H_{19}N_5O_3$	67.76	4.50	16.46
	67	(425.44)	67.60	4.40	16.30
16c	318-20	$C_{29}H_{21}N_5O_3$	71.45	4.34	14.37
	71	(487.51)	71.20	4.10	14.30
16d	320-23	$C_{24}H_{20}N_6O_3$	65.45	4.58	19.08
	70	(440.51)	65.10	4.40	19.00
16e	>330	$C_{23}H_{16}N_6O_2$	67.64	3.95	20.58
	65	(408.42)	67.40	3.80	20.40
16f	>330	$C_{17}H_{13}N_7O_2$	58.79	3.77	28.23
	62	(347.33)	58.50	3.50	28.00
16g	275-78	$C_{28}H_{21}N_5O_4S$	64.23	4.04	13.38
	61	(523.57)	64.10	3.90	13.70
19a	174-75	$C_{26}H_{22}N_4O_6$	64.19	4.56	11.52
	82	(486.48)	64.20	4.60	11.40
19b	242-43	$C_{27}H_{24}N_4O_6$	64.79	4.83	11.19
	72	(500.79)	64.70	4.70	11.00
19c	229-32	$C_{27}H_{24}N_4O_7$	62.79	4.68	10.85
	79	(516.51)	62.60	4.60	11.00
19d	240-42	$C_{26}H_{21}FN_4O_6$	61.90	4.20	11.11
	76	(504.47)	61.60	4.20	11.00
19e	237-39	$C_{26}H_{21}BrN_4O_6$	55.23	3.74	9.91
	80	(565.39)	55.20	3.60	10.00
19f	220-23	$C_{26}H_{20}Cl_2N_4O_6$	56.23	3.63	10.09
	78	(555.37)	56.10	3.60	10.00
20	180-83	$C_{19}H_{20}N_4O_5$	59.37	5.24	14.57
	78	(384.33)	59.50	5.10	14.30

2-[3′-Ethoxycarbonyl-5′-methyl-1′-(4-methylphenyl)pyrazol-4′-yl]imidazo[1,2-*a*]pyridine (13)

A mixture of 4-bromoacetyl-3-ethoxycarbonyl-5-methyl-1-(4-methylphenyl)pyrazole (1.8 g, 5 mmol) and 2-aminopyridine (0.9 g, 10 mmol) in ethanol (20 mL) was refluxed for 2 h. The reaction mixture was cooled, diluted with water and the resulting solid was collected and crystallized from acetone to give **13**.

Synthesis of the Isoxazoles 15a-j

Acetylacetone, benzoylacetone, dibenzoylmethane, acetoacetanilide, benzoylacetonitrile, malononitrile, β-ketosulfones, ethyl cyanoacetate or ethyl acetoacetate (**14a-j**) (5 mmol) was added with stirring to an ethanolic solution of sodium ethoxide obtained by dissolving sodium metal (0.11 g, 5 mmol) in ethanol (20 mL). The hydroximoyl chloride **1** (1.7 g, 5 mmol) was added to the resulting solution, and stirring was continued for 3 h. The reaction mixture was left at room temperature overnight. The resulting solid was filtered off, washed with water, and crystallized from ethanol to give **15a-j**, respectively.

Synthesis of the Pyrazolo[3,4-*d*]pyridazines 16a-g

A mixture the appropriate isoxazoles **15a-g** (5 mmol) and hydrazine hydrate (80%; 1 mL) in ethanol (20 mL) was heated under reflux for 4 h; and the solvent was then evaporated *in vacuo*. The solid was collected and crystallized from ethanol or DMF to give **16a-g**, respectively.

Synthesis of 19a-f and 20

A solution of **1** (1.7 g, 5 mmol) and the appropriate *N*-arylmaleimide or acrylamide (5 mmol) in toluene (25 mL) was refluxed for 20 h. The solvent was evaporated under vacuo. The resulting solid was collected and crystallized from benzene to give **19a-f** and **20**, respectively.

Table 2. Spectral Data of the Products

Compd. No.	IR/cm^{-1} (selected lines)	^{1}H NMR δ/ppm
1	3450 (OH), 1730 (CO ester), 1690 (CO)	1.13 (t, 3H, $CH_3\underline{CH_2}$), 2.41 (s, 3H, $C_6H_4CH_3$-*p*); 2.49 (s, 3H, pyrazole C_5-CH_3); 4.23 (q, 2H, $CH_3\underline{CH_2}$); 7.41 (m, 4H, ArH's) and 10.41 (s, 1H, NO<u>H</u>).
4	3381 (NH), 1712 (CO ester), 1570 (N=O)	
5a	3345 (NH), 1728, 1691 (2 CO)	1.18 (t, 3H, $\underline{CH_3}CH_2$); 2.31 (s, 3H, $C_6H_4CH_3$-*p*); 2.41 (s, 3H, pyrazole C_5-CH_3); 4.23 (q, 2H, $CH_3\underline{CH_2}$) and 7.25-7.69 (m, 9H, ArH's and NH protons).
5b	3328 (NH), 1746, 1661 (2 CO)	1.00 (t, 3H, $\underline{CH_3}CH_2$); 2.42 (s, 3H, $C_6H_4CH_3$-*p*); 2.46 (s, 3H, pyrazole C_5-CH_3); 4.22 (q, 2H, $CH_3\underline{CH_2}$) and 7.26-7.69 (m, 9H, ArH's and NH protons).
7a	3400-2800 (OH, NH), 1733, 1720, 1664 (3 CO)	1.04 (t, 3H, $\underline{CH_3}CH_2$); 2.52 (s, 6H, $C_6H_4CH_3$-*p* and pyrazole C_5-CH_3); 4.09 (q, 2H, $CH_3\underline{CH_2}$; 6.65-7.81 (m, 9H, ArH's and NH) and 10.04 (s, 1H, NO<u>H</u>) and 10.95 (s, 1H, COO<u>H</u>)
7b	3335 (NH), 1732, 1688 (2 CO)	1.25 (t, 3H, $\underline{CH_3}CH_2$); 2.41 (s, 3H, $C_6H_4CH_3$-*p*); 2.44 (s, 3H, pyrazole C_5-CH_3); 3.89 (s, 3H, CH_3-OCO); 4.21 (q, 2H, $CH_3\underline{CH_2}$); 6.91-7.99 (m, 8H, ArH's); 8.43 (s, br, 1H, NH) and 10.12 (s, 1H, NO<u>H</u>).
8	3565 (OH), 1737, 1700 (2 CO)	0.98 (t, 3H, $\underline{CH_3}CH_2$); 2.44 (s, 3H, $C_6H_4CH_3$-*p*); 2.64 (s, 3H, pyrazole C_5-CH_3); 3.96 (q, 2H, $CH_3\underline{CH_2}$) and 7.26-8.38 (m, 9H, ArH's and NO<u>H</u>).
12a	1730 (CO), 1580 (NO)	1.30 (t, 3H, $\underline{CH_3}CH_2$); 2.42 (s, 3H, $C_6H_4CH_3$-*p*); 2.52 (s, 3H, pyrazole C_5-CH_3); 4.24 (q, 2H, $CH_3\underline{CH_2}$) and 7.10-7.80 (m, 8H, ArH's).
12b	1721 (CO), 1537 (NO)	
13	1735 (CO)	
15a	1751, 1690, 1665 (3 CO)	1.25 (t, 3H, $\underline{CH_3}CH_2$); 2.42 (s, 3H, $C_6H_4CH_3$-*p*); 2.49 (s, 3H, pyrazole C_5-CH_3); 2.52 (s, 3H, isoxazole C_5-CH_3); 2.70 (s, 3H, CH_3CO); 4.23 (q, 2H, $CH_3\underline{CH_2}$) and 7.33 (s, 4H, ArH's).
15b	1715, 1690, 1664 (3 CO)	1.25 (t, 3H, $\underline{CH_3}CH_2$); 2.42 (s, 3H, $C_6H_4CH_3$-*p*); 2.49 (s, 3H, pyrazole C_5-CH_3); 2.52 (s, 3H, isoxazole C_5-CH_3); 2.70 (s, 3H, CH_3CO); 4.23 (q, 2H, $CH_3\underline{CH_2}$) and 7.1-7.7 (m, 9H, ArH's).
15c	1733, 1665, 1640 (3 CO)	
15d	3420 (NH), 1730, 1672, 1655 (3 CO)	1.31 (t, 3H, $\underline{CH_3}CH_2$); 2.42 (s, 3H, $C_6H_4CH_3$-*p*); 2.49 (s, 3H, pyrazole C_5-CH_3); 2.52 (s, 3H, isoxazole C_5-CH_3); 2.70 (s, 3H, CH_3CO); 4.20 (q, 2H, $CH_3\underline{CH_2}$) and 7.2-8.2 (m, 9H, ArH's and NH).
15e	2240 (CN), 1743, 1660 (2 CO)	1.32 (t, 3H, $\underline{CH_3}CH_2$); 2.42 (s, 3H, $C_6H_4CH_3$-*p*); 2.49 (s, 3H, pyrazole C_5-CH_3); 4.22 (q, 2H, $CH_3\underline{CH_2}$) and 7.2-7.6 (m, 9H, ArH's).
15f	3345, 3270 (NH_2), 2231 (CN), 1725, 1667 (2 CO)	1.50 (t, 3H, $\underline{CH_3}CH_2$); 2.42 (s, 3H, $C_6H_4CH_3$-*p*); 2.49 (s, 3H, pyrazole C_5-CH_3); 4.42 (q, 2H, $CH_3\underline{CH_2}$; 5.60 (s, br, 2H, NH_2) and 7.3-7.6 (m, 4H, ArH's).
15g	1733, 1679 (2 CO)	1.30 (t, 3H, $\underline{CH_3}CH_2$); 2.42 (s, 3H, $C_6H_4CH_3$-*p*); 2.49 (s, 3H, pyrazole C_5-CH_3); 4.30 (q, 2H, $CH_3\underline{CH_2}$) and 7.2-8.1 (m, 14H, ArH's).
15h	1720, 1667 (2 CO)	1.27 (t, 3H, $\underline{CH_3}CH_2$); 2.42 (s, 6H, two $C_6H_4CH_3$-*p*); 2.49 (s, 3H, pyrazole C_5-CH_3); 4.30 (q, 2H, $CH_3\underline{CH_2}$) and 7.23-7.80 (m, 13H, ArH's).
15i	3370, 3260 (NH_2), 1750, 1730, 1672 (3 CO)	1.29 (t, 3H, $\underline{CH_3}CH_2$); 1.33 (t, 3H, $\underline{CH_3}CH_2$); 2.42 (s, br, 2H, NH_2); 2.47 (s, 3H, pyrazole C_5-CH_3); 2.49 (s, 3H, $C_6H_4CH_3$-*p*); 2.52 (s, 3H, isoxazole C_5-CH_3); 4.28 (q, 2H, $CH_3\underline{CH_2}$); 4.36 (q, 2H, $CH_3\underline{CH_2}$) and 7.30 (s, 4H, ArH's).

Table 2. Continued

15j	1750, 1730, 1673 (3 CO)	1.28 (t, 3H, $\underline{CH_3}CH_2$); 1.34 (t, 3H, $\underline{CH_3}CH_2$); 2.43 (s, 3H, $C_6H_4CH_3$-*p*); 2.49 (s, 3H, pyrazole C_5-CH_3); 2.52 (s, 3H, isoxazole C_5-CH_3); 4.29 (q, 2H, $CH_3\underline{CH_2}$); 4.36 (q, 2H, $CH_3\underline{CH_2}$) and 7.32 (s, 4H, ArH's).
16a	3240 (NH), 1696, 1646 (2 CO)	2.20 (s, 3H, $C_6H_4CH_3$-*p*); 2.45 (s, 3H, pyrazole C_5-CH_3); 2.70 (s, 3H, isoxazole C_5-CH_3); 2.98 (s, 3H, 4-acetylisoxazole); 6.20 (s, br, 1H, NH) and 7.3-7.6 (m, 4H, ArH's).
16b	1693, 1650 (2 CO)	2.35 (s, 3H, $C_6H_4CH_3$-*p*); 2.42 (s, 3H, pyrazole C_5-CH_3); 2.45 (s, 3H, isoxazole C_5-CH_3); 2.70 (s, 3H, 4-acetylisoxazole); 5.90 (s, br, 1H, NH) and 7.0-7.6 (m, 9H, ArH's).
16c	3193 (NH), 1749, 1667 (2 CO)	2.30 (s, 3H, $C_6H_4CH_3$-*p*); 2.54 (s, 3H, pyrazole C_5-CH_3); 5.90 (s, br, 1H, NH) and 7.3-7.8 (m, 9H, ArH's).
16d	3182 (NH), 1735, 1680, 1667 (CO)	2.44 (s, 3H, $C_6H_4CH_3$-*p*); 2.74 (s, 3H, pyrazole C_5-CH_3); 2.58 (s, 3H, isoxazole C_5-CH_3); 7.2-7.6 (m, 9H, ArH's); 10.2 (s, br, 1H, NH) and 12.8 (s, br, 1H, NH).
16e	3430 (NH), 2235 (CN), 1682 (CO)	2.42 (s, 3H, $C_6H_4CH_3$-*p*); 2.50 (s, 3H, pyrazole C_5-CH_3) and 7.1-7.8 (m, 10H, ArH's and NH).
16f	3435 (NH), 2200 (CN), 1692 (CO)	2.42 (s, 3H, $C_6H_4CH_3$-*p*); 2.49 (s, 3H, pyrazole C_5-CH_3); 5.60 (s, br, 2H, NH_2) and 7.2-7.8 (m, 5H, ArH's).
16g	3115 (NH), 1680 (CO)	2.32 (s, 3H, $C_6H_4CH_3$-*p*); 2.45 (s, 3H, pyrazole C_5-CH_3) and 7.2-8.1 (m, 15H, ArH's and NH).
19a	1793, 1737, 1721, 1660 (CO)	1.30 (t, 3H, $\underline{CH_3}CH_2$); 2.42 (s, 3H, $C_6H_4CH_3$-*p*); 2.45 (s, 3H, pyrazole C_5-CH_3); 4.47 (q, 2H, $CH_3\underline{CH_2}$); 5.12 (d, 1H, isoxazoline H-4); 5.69 (d, 1H, isoxazoline H-5) and 7.1-7.4 (m, 9H, ArH's).
19b	1784, 1727, 1713, 1654 (CO)	1.22 (t, 3H, $\underline{CH_3}CH_2$); 2.42 (s, 6H, two $C_6H_4CH_3$-*p*); 2.47 (s, 3H, pyrazole C_5-CH_3); 4.22 (q, 2H, CH_{3CH2}); 5.16 (d, 1H, isoxazoline H-4); 5.84 (d, 1H, isoxazoline H-5) and 7.29-7.54 (m, 8H, ArH's).
19c	1792, 1728, 1710, 1659 (CO)	1.25 (t, 3H, $\underline{CH_3}CH_2$); 2.40 (s, 3H, $C_6H_4CH_3$-*p*); 2.44 (s, 3H, pyrazole C_5-CH_3); 3.77 (s, 3H, $C_6H_4CH_3O$-*p*); 4.20 (q, 2H, $CH_3\underline{CH_2}$); 5.09 (d, 1H, isoxazoline H-4); 5.89 (d, 1H, isoxazoline H-5) and 7.32-7.52 (m, 8H, ArH's).
19d	1780, 1730, 1719, 1650 (CO)	1.28 (t, 3H, $\underline{CH_3}CH_2$); 2.45 (s, 3H, $C_6H_4CH_3$-*p*); 2.50 (s, 3H, pyrazole C_5-CH_3); 4.29 (q, 2H, $CH_3\underline{CH_2}$); 5.10 (d, 1H, isoxazoline H-4); 5.78 (d, 1H, isoxazoline H-5) and 7.21-7.49 (m, 8H, ArH's).
19e	1792, 1732, 1708, 1651 (CO)	
19f	1796, 1736, 1713, 1655 (CO)	
20	3371-3190 (NH_2), 1739, 1700 (2 CO)	1.33 (t, 3H, $\underline{CH_3}CH_2$); 2.40 (s, 3H, $C_6H_4CH_3$-*p*); 2.56 (s, 3H, pyrazole C_5-CH_3); 3.66 (d, 2H, isoxazoline H-4); 4.31 (q, 2H, $CH_3\underline{CH_2}$; 5.16 (t, 1H, isoxazoline H-5); 6.2 (s, br, 2H, NH_2) and 7.1-7.4 (m, 4H, ArH's).

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Key Words

Pyrazoloylhydroximoyl chloride; Quinoxaline; Benzthiadiazine; Benzoxadiazine; Imidazo[1,2-*a*]pyridine; Imidazo[1,2-*a*]pyrimidine; Pyrazolo[3,4-*d*]pyridazine.

REFERENCES

1. Hawking, F. *Experimental Chemotherapy*, 1, Academic Press, New York, **1963**, p. 197.
2. Izum, K.; Kitamikado, T.; Sugiura, S.; Kato, K.; Hori, M.; Fujimura, H. *J. Pharm. Soc. Japan* **1973**, *93*, 1349; [CA: **1974**, 82795b, *80*].
3. Sugiura, S.; Ohno, S.; Ohtani, O.; Izum, K.; Kitamikado,

T.; Asai, H.; Kato, K. *J. Med. Chem.* **1977**, *20*, 80.
4. Sugiura, S.; Kato, K.; Ohno, S.; Ohtani, O.; Wakayama, T. *J. Pharm. Soc. Japan* **1979**, *97*, 719; [CA: **1978**, *6789c*, *88*].
5. Almirante, L.; Polo, L.; Mugnaini, A.; Proviniciali, E.; Rugarli, P.; Gamba, A.; Olivi, A.; Murmann, W. *J. Med. Chem.* **1966**, *9*, 29.
6. Almirante, L.; Polo, L.; Mugnaini, A.; Proviniciali, E.; Rugarli, P.; Biancotti, A.; Gamba, A.; Murmann, W. *J. Med. Chem.* **1965**, *8*, 305.
7. Collins, R. J.; Tang, A. H.; Keasling, H. H. *J. Pharmacol. Exp. Ther.* **1967**, *159*, 428.
8. Preston, P. N. *The Chemistry of Heterocyclic Compounds* Wiley & Sons, New York, **1980**, Vol. 40/II, 531.
9. Parkanyi, C.; Abdelhamid, O. A.; Cheng, J. C. S.; Shawali, A. S. *J. Heterocycl. Chem.* **1984**, *21*, 1029.
10. Abdelhamid, O. A.; Parkanyi, C.; Khaledur, S. M.; Lloyd, W. D. *J. Heterocycl. Chem.* **1988**, *25*, 403.
11. Abdelhamid, O. A.; Khalifa, F. A.; Ghabrial, S. S. *Phosph., Sulfur and Silicon* **1988**, *40*, 41.
12. Abdelhamid, O. A.; Negm, A. M.; Abdeen, T. M. S. *Arch. Pharm.* (Weinheim) **1988**, *321*, 913.
13. Zohdi, H. F.; Khalifa, F. A.; Abdelhamid, A. O.; El-Tourgman, A. A. *J. Chem. Res.* **1991**, (*S*), 322.
14. Abdelhamid, O. A.; Abdou, S. E.; Mahgoub, S. A. *Arch. Pharm. Res.* **1992**, *15*, 317.
15. Abdelhamid, O. A.; Al-Hamidi, A. A. *J. Chin. Chem. Soc.* **1995**, *42*, 83.
16. Mosby, W. L. *Heterocyclic Systems with Bridgehead Nitrogen Atoms* Interscience, New York, **1965**, Part I, 460.
17. Lang, Jr, S. A.; Lin, Y. *Comprehensive Heterocyclic Chemistry*, ed. Katritzky, A.; Rees, C. W. Pergamon, Oxford, **1984**, vol. 6.
18. Shawali, A. S. *J. Heterocycl. Chem.* **1977**, *14*, 375.
19. Osman, T. O. *M. Sc. Thesis*, Cairo University, **1996**.