Some Acetyl Substituted Pyrazolo[1,5-*a*]pyrimidin-5(4*H*)one Derivatives

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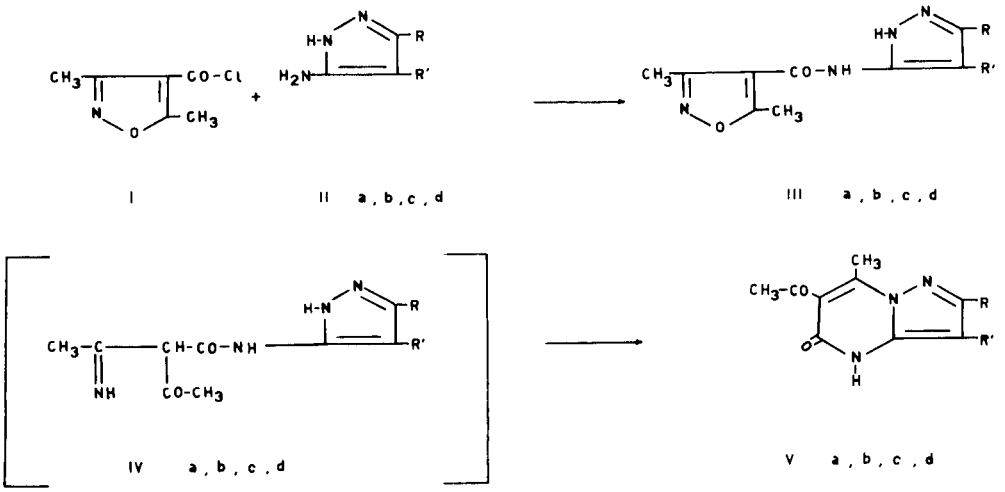
As part of our interest in the synthesis and pharmacological activity of polycondensed heterocycles we explored a facile synthetic route to acetyl-substituted pyrazolo[1,5-*a*]pyrimidin-5(4*H*)one derivatives. The reaction between amines IIa,b,c,d and 3,5-dimethylisoxazole-4-carboxylic acid chloride (I) in pyridine under mild conditions afforded amides IIIa,b,c,d in good yield. Catalytic hydrogenation on W-2 Raney Nickel of IIIa,b,c,d gave directly the desired acetyl derivatives Va,b,c,d (Scheme I). The assigned structures of Va,b,c,d were supported by elemental analysis and were in agreement with spectroscopic data. The uv spectra were similar to that of pyrazolo[1,5-*a*]-pyrimidin-5(4*H*)one derivatives (I) with the expected modification due to the substituents. Infrared spectra determined in potassium bromide disks showed ν C=O at 1640 and 1680 cm^{-1} due to the cyclic carbonyl group and acetyl group respectively and multiple bands in the 3 μ region due to the intermolecular bonded NH stretching. Nmr spectra exhibited a broad singlet (1H) downfield due to NH in addition to other signals for substituents protons.

In order to evaluate the usefulness of this reaction for synthesis of acetyl substituted 7*H*-thiazolo[3,2-*a*]pyrimidin-7-one derivatives XIa,b,c, the amides VIIa,b,c obtained from condensation of amines VIa,b,c with I, were examined (Scheme II). Reductive elevage with W-2 Raney Nickel of the isoxazole ring of VIIa,b,c afforded white crystalline products VIIIa,b,c in high yield whose structural assignment were based on nmr and ir spectra. In fact, the nmr spectra determined in DMSO-d_6 exhibited an enolic proton signal at 8.30-8.50 δ exchangeable with deuterium oxide, and the ir spectra showed an amide I absorption band below 1660 cm^{-1}. Repeated attempts at ring closure of VIIIa,b,c under many different conditions failed to give XIa,b,c. Instead, refluxing compounds VIIIb,c in ethanol with hydrochloric acid readily afforded 2-acetoacetamido derivatives IXb,c. Compound VIIIa was recovered unchanged after refluxing 1 hour and after prolonged heating only an intractable material was obtained. The structures of the products IXb,c were confirmed by analytical and spectroscopic data (ir, nmr) which suggest that these compounds exist in the β-di-

SCHEME I



SCHEME II

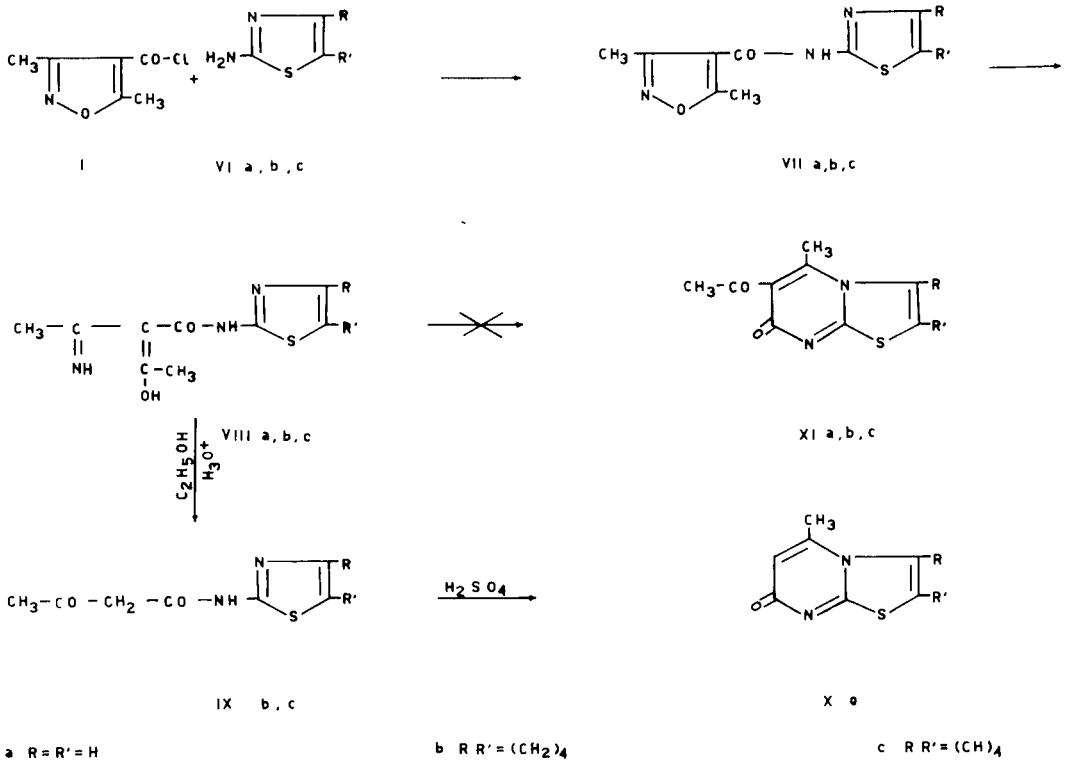
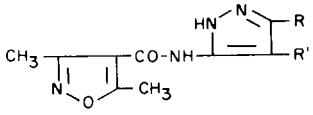
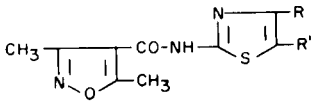


TABLE I

N-(Pyrazol-5-yl)- and *N*-(thiazol-2-yl)-3,5-dimethyl-4-isoxazolecarboxamides.



III



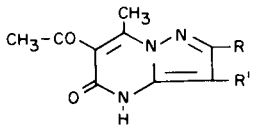
VII

	R	R′	M.p., °C	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIIa	C_6H_5	H	256-257°	$C_{15}H_{14}N_4O_2$ (a)	63.82	5.00	19.85	64.13	5.04	20.16
IIIb	$(CH_2)_4$		246-248°	$C_{13}H_{16}N_4O_2$ (b)	59.98	6.20	21.53	59.93	6.21	21.20
IIIc	$(CH_2)_5$		214-216°	$C_{14}H_{18}N_4O_2$ (c)	61.29	6.61	20.43	61.29	6.86	20.28
IIId	$(CH)_4$		210-212°	$C_{13}H_{12}N_4O_2$ (d)	60.93	4.72	21.87	60.75	4.65	21.77
VIIa	H	H	178-180°	$C_9H_9N_3O_2S$ (e)	48.43	4.06	18.83	48.65	4.05	18.48
VIIb	$(CH_2)_4$		175-178°	$C_{13}H_{15}N_3O_2S$ (f)	56.31	5.45	15.16	56.56	5.45	15.16
VIIc	$(CH)_4$		208-210°	$C_{13}H_{11}N_3O_2S$ (g)	57.14	4.06	15.38	57.34	4.05	15.65

(a) Ir 3300 and 3240 (2 x NH), 1660 cm^{-1} (CO); nmr 2.31 δ (3H, s, CH_3), 2.51 δ (3H, s, CH_3), 6.94 δ (1H, s, pyrazole CH), 7.30-7.82 δ (5H, m, C_6H_5), 10.50 δ (1H, s, pyrazole NH), 12.83 δ (1H, s, amidic NH). (b) Ir 3420 and 3280 (broad) (2 x NH), 1680 cm^{-1} (CO); nmr 1.40-2.80 δ (14H, m, $(CH_2)_4$ and 2 x CH_3), 9.83 δ (1H, s, pyrazole NH), 12.10 δ (1H, s, amide NH). (c) Ir 3500 and 3240 (broad) (2 x NH), 1660 cm^{-1} (CO); nmr 1.30-2.90 δ (16H, m, $(CH_2)_5$ and 2 x CH_3), 9.68 δ (1H, s, pyrazole NH), 12.20 δ (1H, s, amidic NH). (d) Ir 3420 and 3240 (broad) (2 x NH); 1660 cm^{-1} (CO); nmr 2.40 δ (3H, s, CH_3), 2.63 δ (3H, s, CH_3), 6.80-8.20 δ (4H, m, C_6H_4) 10.55 δ (1H, s, pyrazole NH), 12.87 δ (1H, s, amide NH). (e) Ir 3180 (broad) (NH), 1680 cm^{-1} (CO); nmr 2.40 δ (3H, s, CH_3), 2.67 δ (3H, s, CH_3), 7.17 δ (1H, d, $J_{H4,5}$ = 4.0 Hz), 7.57 δ (1H, d, $J_{H5,4}$ = 4.0 Hz) ~12.37 δ (1H, broad, amide NH). (f) Ir 3180 (broad) (NH) 1680 cm^{-1} (CO); nmr 1.60-2.90 δ (14H, m,$(CH_2)_4$ and 2 x CH_3), ~11.90 δ (1H, broad, NH). (g) Ir 3340 (NH), 1660 cm^{-1} (CO); nmr 2.52 δ (3H, s, CH_3), 2.78 δ (3H, s, CH_3), 7.20-8.30 δ (4H, m, C_6H_4), ~11.50 δ (1H, broad, NH).

TABLE II

6-Acetyl-7-methylpyrazolo[1,5-*a*]pyrimidin-5(4*H*)one Derivatives



	R	R′	M.p., °C	Formula	V	Analysis Calcd. C	H	N	Found C	H	N
Va	C_6H_5	H	250-251°	$C_{15}H_{13}N_3O_2$ (a)		67.40	4.90	15.72	67.58	4.90	15.72
Vb	$(CH_2)_4$		280-282°	$C_{13}H_{15}N_3O_2$ (b)		63.66	6.16	17.13	63.79	6.00	16.92
Vc	$(CH_2)_5$		268-270°	$C_{14}H_{17}N_3O_2$ (c)		64.84	6.61	16.21	64.66	6.81	16.39
Vd	$(CH)_4$		323-325°	$C_{13}H_{11}N_3O_2$ (d)		64.72	4.60	17.42	64.99	4.56	17.75

(a) Uv λ max nm log ε 308 (4.26) 244 (4.15); ir (potassium bromide) 1640 and 1680 cm^{-1} (2 x CO); nmr 2.52 δ (3H, s, CH_3), 2.58 δ (3H, s, CH_3), 6.32 δ (1H, s, H at C_3), 7.20-8.00 δ (5H, m, C_6H_5), ~9.65 δ (1H, broad, NH). (b) Uv λ max nm log ε 300 (3.97) 250 (4.17); ir (potassium bromide) 1640 and 1680 cm^{-1} (2 x CO); nmr 1.40-2.80 δ (14H, m, $(CH_2)_4$ and 2 x CH_3), ~12.27 δ (1H, broad, NH). (c) Uv λ max nm log ε 300 (4.08) 250 (4.29); ir (potassium bromide) 1640 and 1680 cm^{-1} (2 x CO); nmr 1.20-2.90 δ (16H, m, $(CH_2)_5$ and 2 x CH_3), ~12.00 δ (1H, broad, NH). (d) Uv λ max nm log ε 294 (4.32) 251 sh (4.00) 232 sh (4.19); ir (potassium bromide) 1640 and 1680 cm^{-1} (2 x CO); nmr 2.50 δ (3H, s, CH_3), 2.60 δ (3H, s, CH_3), 6.70-8.00 δ (4H, m, C_6H_4), ~13.42 δ (1H, broad, NH).

carbonyl form. In fact, ir spectra showed two strong absorption peaks at 1650 cm^{-1} (amidic CO) and 1700 cm^{-1} (ketonic CO); nmr spectra (DMSO-d_6) exhibited methylene proton signals at 3.70-3.82 δ but no methine signal. Furthermore, compound IXc was converted by action of sulphuric acid into Xc as was shown with an authentic sample (2).

Several of the compounds listed in the Tables I and II were tested by Bristol Laboratories, Syracuse, N. Y. However, none showed encouraging biological activities.

EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting point apparatus and are uncorrected. Infrared spectra were determined in Nujol mull (unless otherwise specified) with a Perkin-Elmer infracord 137 spectrophotometer; ultraviolet spectra were determined in methanol solution with a Beckmann DB recording spectrophotometer. The nmr spectra (DMSO-d_6) were obtained with a Jeolco/C-60H spectrometer (TMS as internal reference).

General Procedure for the 4-Isoxazolecarboxamide Derivatives.

A solution of 10 mmoles of IIa (3), b (4), c (5), d (6) VIa (7), b (8), c in pyridine (50 ml.) was treated with 10 mmoles of 3,5-dimethylisoxazole-4-carboxylic acid chloride (9). After stirring at rt for 24 hours, the solution was evaporated under vacuum; the residue was triturated with aqueous sodium hydroxide (20%) (40 ml.) and after standing at rt for 12 hours, the solution addition of aqueous saturated ammonium chloride gave a precipitate which was collected and recrystallized from ethanol (yield 58-60%). The compounds obtained by this method are listed in Table I.

General Procedure for Pyrazolopyrimidine and Pyrimidoindazole Derivatives.

A mixture of 3 mmoles of III (a,b,c,d), 300 ml. of ethanol and *ca.* 2 g. of W-2 Raney Nickel (10) was hydrogenated in a Parr apparatus at 45-50 psi for 3 hours at room temperature. Removal of the catalyst and evaporation of ethanol left the title compounds, yield 78-80% after recrystallization from ethanol. The compounds obtained by this method are listed in Table II.

Hydrogenation of the Thiazole and Benzothiazole Amides. General Procedure.

A mixture of 3 mmoles of VII (a,b,c), 300 ml. of ethanol and *ca.* 2 g. of W-2 Raney Nickel (10) was hydrogenated in a Parr apparatus at 45-50 psi for 3 hours at rt. Removal of the catalyst and evaporation of ethanol left the reduced products, yield 70-72%, after recrystallization.

3-Hydroxy-2-(1-iminoethyl)-*N*-2-thiazolyl-2-butenamide (VIIIa).

The product melted at 173-175° dec. (ethanol); ir multiple bands in 3 μ region and 1650 cm^{-1} (CO); nmr 2.02 δ (3H, s, CH_3), 2.04 δ (3H, s, CH_3), 7.27 δ (1H, s, $J_{H4,5} \cong 4.0$ Hz), 7.57 δ (1H, d, $J_{H5,4} \cong 4.0$ Hz), ~8.40 δ (1H, broad, OH, ~10.50 δ (1H, braod = NH), ~12.30 δ (1H, broad, amide NH).

Anal. Calcd. for $C_9H_{11}N_3O_2S$: C, 48.00; H, 4.92; N, 18.66. Found: C, 48.39; H, 5.06; N, 18.43.

3-Hydroxy-2-(1-iminoethyl)-*N*-(4,5,6,7-tetrahydro-2-benzothiazolyl)-2-butenamide (VIIIb).

The product melted at 170-173° dec. (ethanol); ir multiple bands in 3 μ region and 1650 cm^{-1} (CO), nmr 1.50-3.00 δ (14H, m, $(CH_2)_4$ and 2 x CH_3), ~8.30 δ (1H, broad OH), ~ 10.50 δ (1H, broad, =NH), ~11.90 δ (1H, broad, amide NH).

Anal. Calcd. for $C_{13}H_{17}N_3O_2S$: C, 55.90; H, 6.14; N, 15.05. Found: C, 55.78; H, 5.98; N, 14.81.

N-2-Benzothiazolyl-3-hydroxy-2-(1-iminoethyl)-2-butenamide (VIIIc).

The product melted at 305-307° (ethanol); ir multiple bands in 3 μ region and 1650 cm^{-1} (CO); nmr 2.12 δ (3H, s, CH_3), 2.15 δ (3H, s, CH_3), 7.20-8.30 δ (4H, m, C_6H_4) ~8.50 δ (1H, broad, OH), ~ 10.50 δ (1H, broad, =NH), ~ 12.50 δ (1H, broad, amide NH).

Anal. Calcd. for $C_{13}H_{13}N_3O_2S$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.95; H, 4.86; N, 14.96.

2-Acetoacetamidotetrahydrobenzothiazole (IXb) and 2-Acetoacetamidobenzothiazole (IXc).

To a solution of 10 mmoles of VIIIb,c in ethanol (50 ml.) was added 2 ml. of ethanol saturated with hydrochloric acid. After refluxing 1 hour the ethanol was removed under vacuum and the residue was mixed with water (100 ml.) the precipitate was collected and recrystallized, yield 70-72%.

Compound IXb.

The product melted at 194-195° (benzene); uv λ max nm log ε 284 (4.06) 215 (3.75); ir 1650 and 1700 cm^{-1} (2 x CO); nmr 1.60-2.90 δ (11H, m, $(CH_2)_4$ and CH_3), 3.70 δ (2H, s, CH_2), 12.20 δ (1H, broad, NH).

Anal. Calcd. for $C_{11}H_{14}N_2O_2S$: C, 55.45; H, 5.92; N, 11.76. Found: C, 55.64; H, 5.95; N, 11.71.

Compound IXc.

The product melted at 222-224° (benzene); uv λ max nm log ε 298 (4.12) 288 (4.16) 280 (4.17) 244 (3.92) 224 sh (4.22); ir 1650 and 1700 cm^{-1} (2 x CO); nmr 2.28 δ (3H, s, CH_3), 3.82 δ (2H, s, CH_2), 7.20-8.20 δ (4H, m, C_6H_4), 12.46 δ (1H, broad, NH).

Anal. Calcd. for $C_{11}H_{10}N_2O_2S$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.51; H, 4.30; N, 11.97.

4-Methyl-2*H*-pyrimido[2,1-*b*]benzothiazol-2-one (Xc).

2-Acetoacetamidobenzothiazole was carefully added to concentrated sulphuric acid at room temperature. After 46 hours the solution was poured on ice, basified with aqueous ammonia and extracted with chloroform, evaporation of which gave Xc, m.p. 246-248° (lit. 244-245°) (ethanol), not depressed on admixture with an authentic specimen (2).

Anal. Calcd. for $C_{11}H_8N_2OS$: N, 12.96. Found: N, 12.71.

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