Synthesis of Certain 3,5,7-Disubstituted Pyrazolo[3,4-*e*][1,3]oxazines. Derivatives of a New Heterocyclic Ring System

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The synthesis of several 3,5,7-trisubstituted pyrazolo[3,4-*e*][1,3]oxazines by ring annulation of the appropriately substituted pyrazoles is described.

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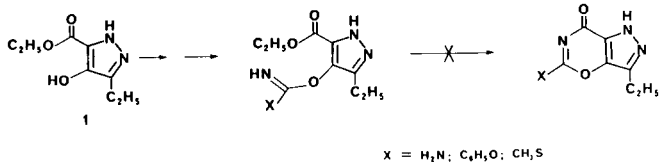
A number of purines, purine nucleosides and purine-like nucleoside antibiotics (*e.g.*, tubercidin, sangivamycin, toyocamycin, formycin (formycin B, *etc*) have exhibited [1-10] significant chemotherapeutic and biological activity. Numerous investigators, including our laboratory, have reported [1-10] on their attempts to increase the chemotherapeutic and biological activity of these nucleosides by selective chemical modifications of the heterocyclic moieties. These modifications have included simple transpositions of atoms, replacement of a methine group with a nitrogen atom, replacement of a nitrogen atom with a methine group, methylation of a ring nitrogen, *etc.* These chemical modifications of active nucleosides have produced definite changes in their chemotherapeutic and biological activity. In fact, it would appear that the major factors may be steric, electronic and/or the specific arrangement or juxtaposition of atoms in the heterocyclic moiety and than electronic effects may be very important. One method for changing the electron density and distribution in the heterocyclic moiety is to attach specific exocyclic groups at certain positions of the ring system. However, this introduces the problem of trying to ascertain if the observed effect is due to electronic considerations or to a steric factor. To preclude this problem, we elected to insert an oxygen atom for a nitrogen atom in the pyrimidine ring of certain bicyclic compounds. This will produce a definite change in the electron density of the heterocycle. This assumption is based on the change in p*K*a observed between uridine (p*K*a = 9.2) or pseudouridine (p*K*a = 9.0) and oxazinomycin (p*K*a = 6.96) where a ring nitrogen has been replaced by an oxygen atom. For our initial studies using this rationale, we elected to concentrate on the synthesis of pyrazolo[3,4-*e*][1,3]oxazines. These specific compounds can be viewed as analogs of the aglycon of the *C*-nucleoside antibiotics formycin, formycin B and oxoformycin B.

Two approaches were investigated in our attempts to prepare this series of compounds. The first approach used 4-hydroxy-5(3)-ethyl-3(5)-carboethoxypyrazole (**1**) [11] as our starting material. The reaction of **1** with cyanogens or amidines should have resulted in a ring annulation by a nucleophilic attack of the imino group of the intermediate on the carboethoxy group [12]. However, there was no evidence of ring closure under the reaction conditions employed in our laboratory.

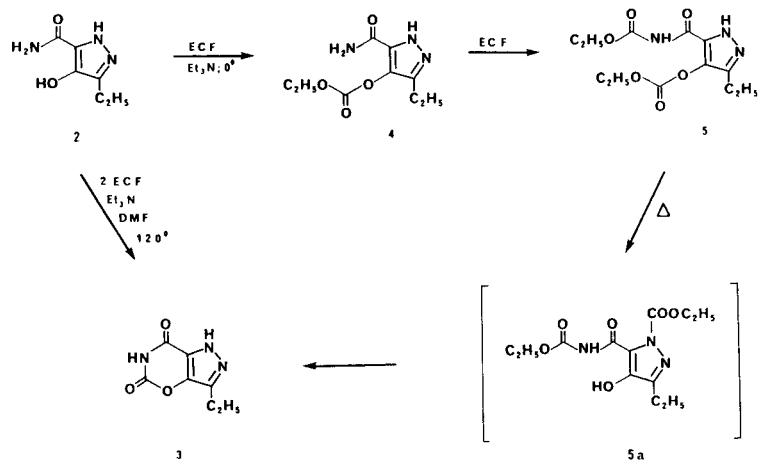
For our second approach, we employed 3(5)-ethyl-4-hydroxypyrazole-5(3)-carboxamide (**2**) [11] as our starting material. Ring annulation of **2** using reagents such as bromocyanogen, chloroformamidine [13] *S*-methylthiourea,



Scheme 1

etc., were unsuccessful. We subsequently found that ethyl chloroformate (ECF) in dimethylformamide containing triethylamine [14] would effect a ring annulation of **2** to furnish 3-ethylpyrazolo[3,4-*e*][1,3]oxazin-5,7-dione (**3**) in 45% yield. However, we were unable to obtain acceptable yields of other 5,7-derivatives of **3** starting directly from **2**. We presumed that these difficulties were related to the tautomeric character of **2** and the facile O → N rearrangement of the intermediate *O*-derivatives as well as to the low stability of the newly formed C-O bond.

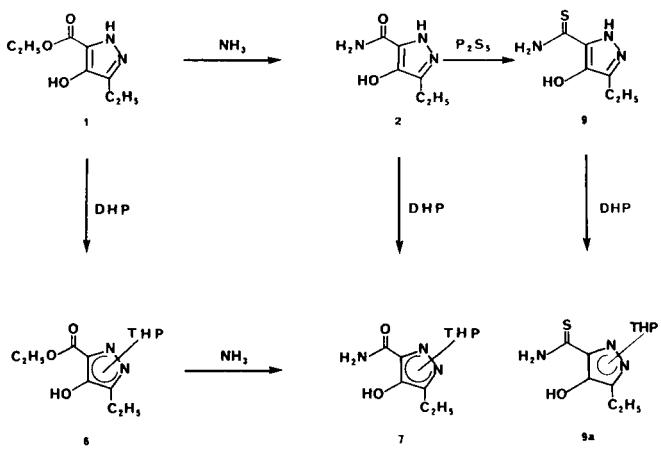
Treatment of **2** with ethyl chloroformate (ratio 1:1) furnished a product which we presumed was **4** since it gave a negative ferric chloride test for phenolic hydroxyl group, a strong peak in the ir spectrum at 1770 cm^{-1} and the expected ^1H nmr spectral data. When an excess of ethyl chloroformate and triethylamine was used at 0-5°, the diacyl derivative **5** of **2** was obtained. The ^1H nmr spectrum of **5** in deuterated chloroform showed two signals at δ 11.8 and 9.2 which were assigned to the N-1 hydrogen and CONHCO moieties, respectively, and signals at 4.25 (q, 4H, OCH_2) 2.65 (q, 2H, CH_2), 1.3 (m, 9H, CH_3) which supported the *O*-acylated structure **5**. However, when the reaction was allowed to continue for several hours, a positive ferric chloride test was again observed which indicated that a free hydroxyl group had been regenerated. A successful ring closure occurred when a two-fold excess of eth-



Scheme 2

yl chloroformate was added to the dimethylformamide solution of **2** and triethylamine at $-10°$ followed by a gradual heating of the reaction mixture and then heating at reflux for 2-3 hours. It would appear that some of the excess ethyl chloroformate serves as a protective group and is later removed during the work-up procedure.

On this *a priori* assumption, we elected to block the N-1 position in an effort to avoid or reduce this type of complication and also to find a more facile and general way to effect the desired ring closing. In this context, we examined acylating agents which would provide a better leaving group as the protective group for blocking the N-1 position. 2,3-Dihydropyran (DHP) was the reagent we finally selected for protection of the pyrazole ring because of its apparent selectivity with OH and NH nucleophiles [15-17], stability under basic conditions and lability under very mild acid conditions [16,18]. 1,1'-Carbonyldiimidazole (CDI) and the corresponding thioanlaog (TCDI), which have been successfully employed for various ring closures [19,20], were selected as the acylating reagents, for our initial studies in this area.

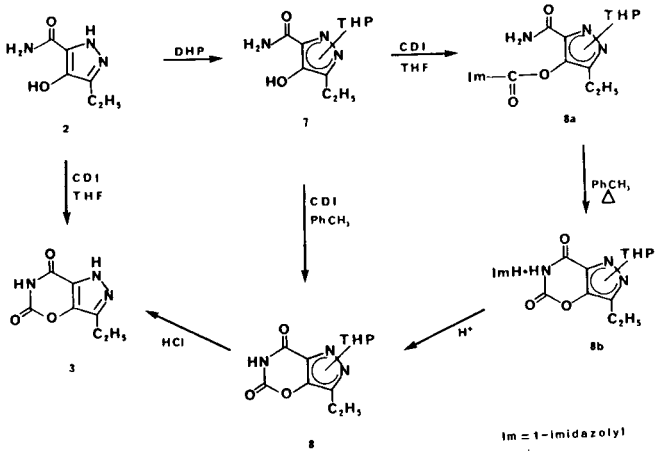


Scheme 3

Though there are two nucleophilic centers in **1** or even three in **2** and **9**, we found that the pyrazole ring of these compounds may be selectively protected by dihydropyran under mild acid catalysis. The protected derivatives **6**, **7** and **9a** have been obtained using slightly modified literature procedures [16,18]. Compounds **6**, **7** and **9a** showed a positive reaction with ferric chloride as well as the correct ir, ^{1}H nmr and ms spectra. In contrast to some reported THP-protected purines (obtained as single isomers), **6** and **7** were obtained as mixtures of two isomers as ascertained by tlc and ^{1}H nmr. The two isomers of **6** (N-1 and N-2 THP derivatives) were separated by column chromatography. Each isomer was chromatographically pure by tlc and although they gave essentially the same elemental analysis they possessed different mp and spectral data (uv, ^{1}H nmr, ^{13}C nmr). One of the isomers showed a substantial downfield chemical shift for the 2'-proton signal ($\Delta\ \delta = 0.57$ ppm). This downfield shift is related to the deshielding effect of an adjacent carboethoxy group and allowed us to make structural assignments to both isomers. According to previous studies [21,22] thiocarboxamido and carboxamide groups may deshield a neighboring anomeric proton ($\Delta\ \delta = 0.2$ to 0.4 ppm) due to an anisotropic effect. The two isomers also exhibit different patterns for the C-3, C-4 and C-5 atoms in the ^{13}C nmr spectra. This has proved to be a very useful tool for determining the position of the tetrahydropyranyl group during further transformations and in other structurally similar compounds. However, for our purpose, the isomeric mixture was used for subsequent reactions without effecting a separation of the isomers.

Unlike ethyl chloroformate, CDI reacted very readily with **2** and **7** in aprotic solvents at reflux (Scheme 4). Compound **8a** was the first product formed in the reaction of **7**

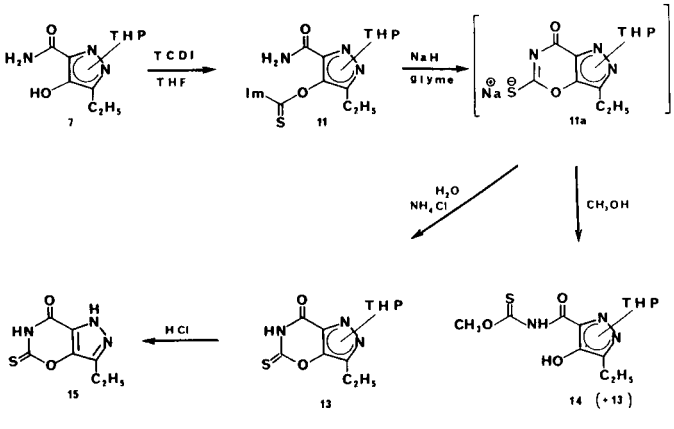
with CDI. The ^{1}H nmr spectrum of **8a** showed three signals for the imidazole ring protons at 8.45, 7.5 and 7.15 ppm as well as signals assigned to an amino group at 7.28



Scheme 4

and 7.50 ppm. However, the spectrum of **8b** revealed only two signals for the aromatic protons of the imidazole cation at 7.10 (s, 2H, $C_{5,4}$-H) and at 7.72 (s, 1H, C{-H). Treatment of **8b** with ammonium hydroxide was followed by treatment with a cation exchange resin (Amberlite, IR-120, H^+) to precipitate pure **8**. We subsequently found that a reaction of **7** with CDI in toluene gave a 45% yield of **8**. Deprotection of **8** furnished compound **3** which was identical to **3** obtained directly from **2**.

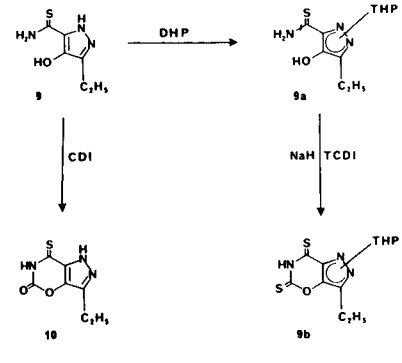
In contrast to CDI, the reaction of 1,1'-thiocarbonyldiimidazole (TCDI) with **2** gave a complicated mixture of compounds. However, reaction of TCDI with **7** in tetrahydrofuran at reflux furnished compound **11** as the only major product. Increasing the temperature of the reaction mixture either did not result in a ring closure or gave complicated mixtures. Sodium hydride has been previously used to increase the nucleophilicity of the carboxamide



Scheme 5

group and in this case has effected a ring closure of **11** to **13**. A solution containing **11** in glyme with sodium hydride was heated at reflux to furnish **13** as a *major* product. A problem which we had anticipated, and indeed encountered in this study, was the instability of the oxazine ring which required special attention. Using a methanol-water solution for our work-up, resulted in a ring opening and gave a mixture of **13** and **14**. A singlet at δ 4.2 in the ^{1}H nmr spectrum was assigned to the methoxy protons and signals at 9.8 and 7.1 (OH, NH) provided additional proof for the proposed structure of **14**. The mass spectrum showed a parent ion of m/z 313 and a characteristic pattern for the open-chain structure fragmentation. (We also used the classical test with ferric chloride to verify ring closure or integrity at each synthetic step). Compound **13** was obtained by taking up the solid residue **12**, after glyme evaporation, in chloroform followed by treatment with a cold saturated ammonium chloride-water solution. The ^{1}H nmr spectrum of **13**, purified by column chromatography, revealed a broad singlet at 9.98 (NH) and characteristic signals for the tetrahydropyranyl and ethyl groups. A high value for the carbonyl absorption (1720 cm^{-1}) in the ir spectrum of **13** is also very characteristic and may be the result of a competition for the unshared electron pair of the ring nitrogen (N_6) between the carbonyl and thiocarbonyl groups [23]. Deblocking of **13** furnished 3-ethylpyrazolo[3,4-*e*][1,3]oxazin-7-one-5-thione (**15**).

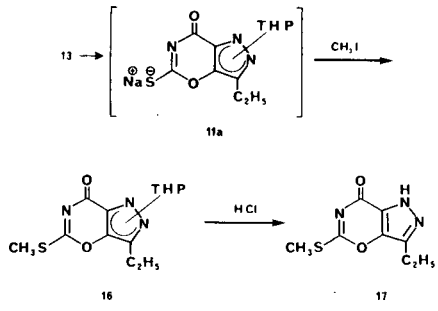
When the thioamide compound **9** was allowed to react with CDI in tetrahydrofuran at reflux, the bicyclic compound **10** was obtained in approximately 80% yield. The reaction of **9** with TCDI proved to be as unsuccessful as when TCDI was reacted with **2**. However, the protected thioamide **9a** reacted very readily with TCDI and furnished 3-ethylpyrazolo[3,4-*e*][1,3]oxazin-5,7-dithione (**9b**). Methylation of **10** with methyl iodide furnished a mixture of the mono and dimethyl derivatives of **10**.



Scheme 6

Exocyclic methylthio groups have been found to function very effectively as leaving groups in the purine series [24]. In our case, we expected to observe a facile displacement of a methylthio group at the C-5 position because of the strong −I effect of the adjacent ring oxygen atom. This prompted us to prepare the appropriate methylthio

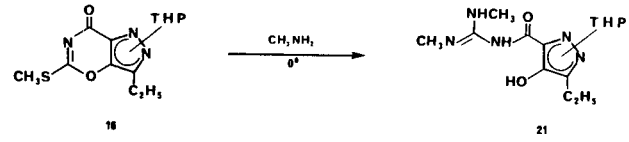
derivative as a precursor for the guanine analog. Methylation of the sodium salt **12** with methyl iodide furnished the methylthio derivative **16** in 54% yield. Subsequent de-



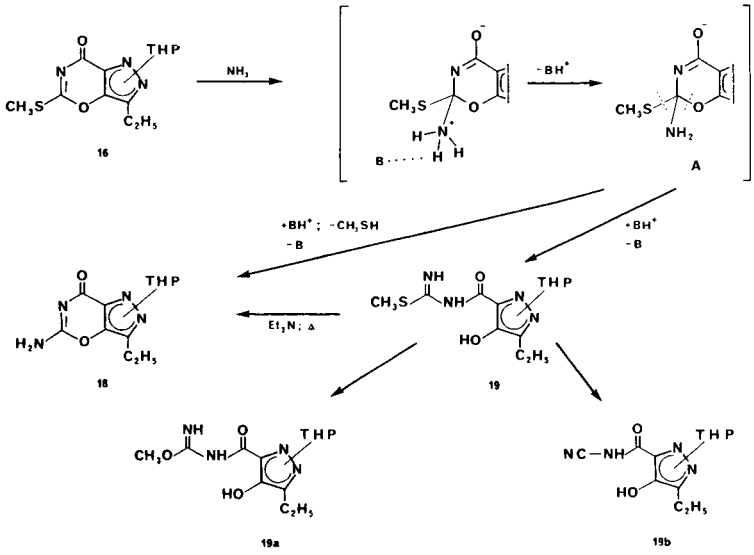
Scheme 7

blocking, using our standard procedure, gave 3-ethyl-5-methylthiopyrazolo[5,4-*e*][1,3]oxazin-7-one (**17**). Aminolysis is usually accomplished by using either liquid ammonia or a methanol ammonia solution. However, treatment of **16** by either method gave complicated reaction mixtures. These mixtures showed a positive ferric chloride test which would indicate that some ring opening had taken place. Some of the minor side-products from these mixtures were separated and analyzed. Compound **19b** was obtaind from the reaction of **16** with liquid ammonia at $-50°$ and revealed a strong absorption at 2160 cm^{-1} ($C\equiv N$) with a characteristic low value for the carbonyl absorption (1620-1600 cm^{-1}). There were no signals observed in the ^1H nmr spectrum of **19b** which could be attributed to a methylthio group, however, when the reaction was conducted in methanol or a methanol-methylene chloride mixture, compound **19a** was the major side-product. The ^1H nmr spectrum of **19a** revealed a signal at δ 3.9 which could be attributed to a CH_3O group and a broad absorption at δ 9.8-9.2 which was attributed to NH and OH hydrogens. When the reaction was conducted in methylene chloride, compound **19**, was the major product. The ^1H nmr spectrum of **19** showed a sharp absorption at δ 2.5 which could be attributed to the SCH_3 group and a broad absorption at δ 9.5-9.0 (NH, OH). The mass spectra of **19a** and **19** gave peaks for the molecular ions at 296 and 312 m/z, respectively. According to the assumed mechanism for this reaction, the nucleophilic substitution was accompanied by subsequent ring opening (a competition between the two leaving groups takes place in **A**.) Therefore, two mechanisms S_N(AE) and ANRORC may be involved in this reaction [25,26]. When compound **19** was dissolved in benzene and the solution heated at reflux in the presence of triethylamine, tlc showed a slow transformation of **19** into **18**.

After this preliminary study, the amination of **16** was conducted as a two step reaction in dry methylene chloride containing triethylamine. The first step involved passing ammonia (gas) through the reaction mixture at 10° and the sealed flask was then allowed to stand at room temperature until we observed a complete disappearance of **16**. The second step was to heat the reaction mixture at reflux for 4 hours in order to convert **19** into **18**. Longer reaction times usually resulted in excessive decomposition. This procedure allowed us to simplify the work-up and purification process which increased the yield of **18** from 15-20% to 65%.



Scheme 9



Scheme 8

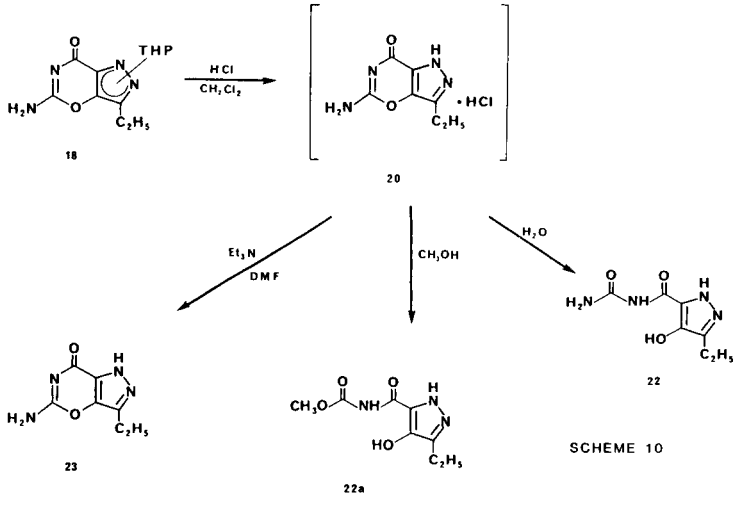
The only product we could isolate from a reaction of **16** with methylamine was **21**. The formation of this compound most likely occurs *via* an intermediate similar to **19** and this was apparently followed by a subsequent reaction of the intermediate with another mole of methylamine.

One of the more common procedures used to remove a THP blocking group from a heterocyclic ring nitrogen atom is treatment with a water or methanol solution of hydrogen chloride. The conditions used were very diverse and varied from a few drops of 0.1 *N* hydrochloric acid at room temperature [18] to heating at reflux for 18 hours in a methanol:concentrated hydrochloric acid:water, 8:3:1 solution [27]. Our initial investigations involved the deblocking of **18** with 1 *N* hydrochloric acid in a methanol-water solution. However, the reactions were very slow and usually resulted in a complicated mixture of compounds which were difficult to separate. When the hydrogen chloride concentration was sharply increased, a mixture of two products was obtained. The minor product, more soluble in chloroform, showed a strong singlet at δ 3.7 which was assigned to the CH_3O group of **22a**. The major product was purified by hplc and was also successfully deblocked according to ^1H nmr spectral data. However, elemental analysis showed that the product [22] contained what appeared to be an additional one mole of water while the ^1H nmr spectrum indicated that perhaps what we had in hand was a ring opened product. The mass spectrum of **22**, as well as a ferric chloride test, confirmed that ring opening of **20** to afford **22** had indeed taken place. We subsequently found that when hydrogen chloride gas was passed through a cold methylene chloride solution containing **18** for 2-3 minutes, a white precipitate (probably a mixture of **20** and **23**) was obtained. Treatment of the solid with dimethyl formamide containg triethylamine furnished pure **23**. A similar procedure was then employed to obtain the deblocked derivatives **3**, **9b**, **15**, and **17**.

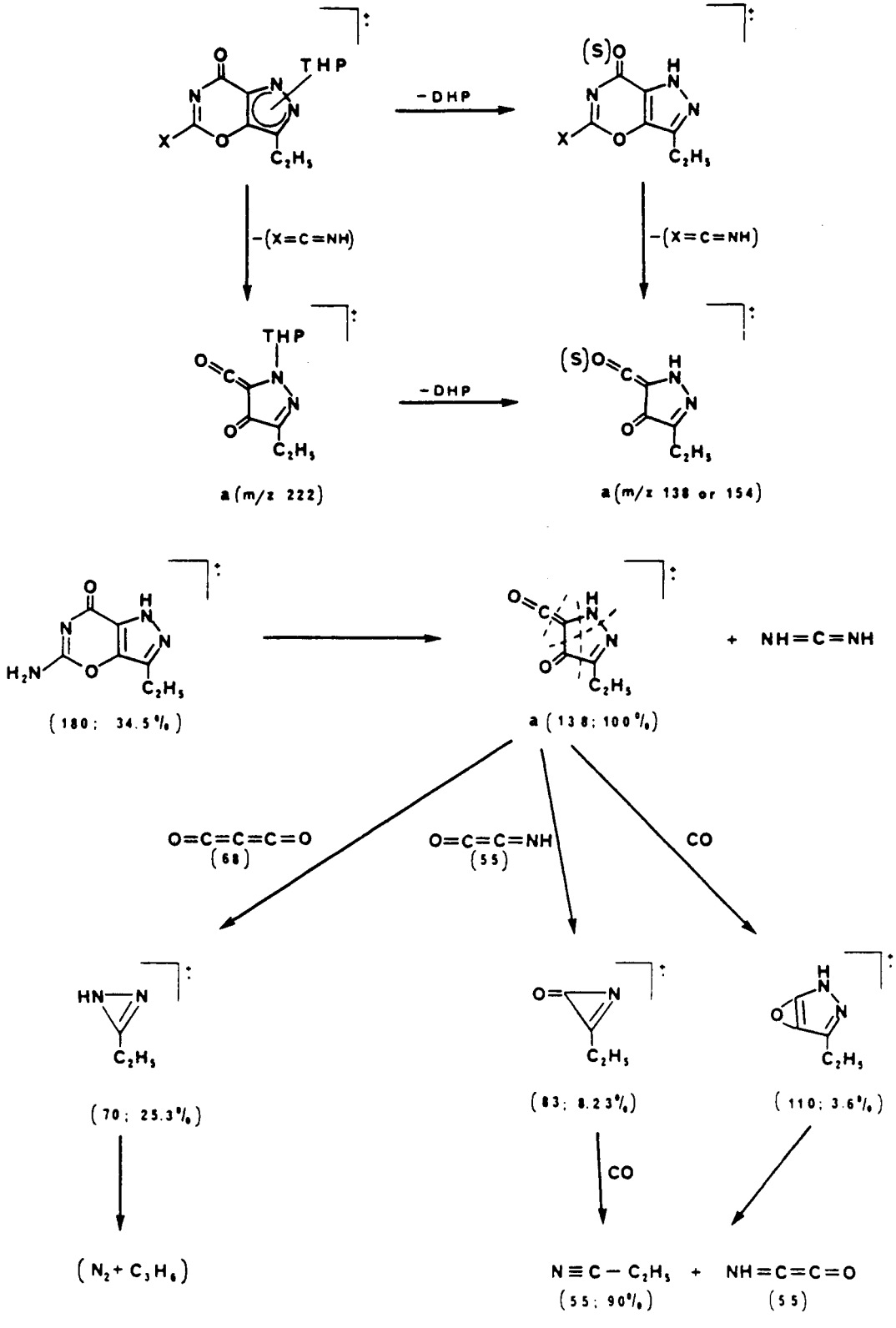
During this study, we found that the mass spectra of these 3,5,7-trisubstituted pyrazolo[3,4-*e*][1,3]oxazines are very characteristic and similar to other bicyclic 1,3-azines [28,29]. The molecular ions (or M + 1) are detectable but exhibited a variation in intensity from 16 to 58% and were much lower for the THP-protected compounds (1-11%). It appears that a one step primary cleavage of the retro-Diels-Alder type results in the formation of "dienophile" (X = C = NH) and "diene" (**a**) fragments (Scheme 11). A peak at m/z 138 (or 222 for the THP protected series) is one of the major peaks. According to this fragmentation pattern, compounds **3**, and **15**, and **10**, gave the fragments **a** m/z 138 and 154, respectively. The peak at m/z 85 was, as a rule, the dominant peak (100%) for the THP-protected compounds.

Assumed pathways of fragmentation for **a** are shown in Scheme 11. Unlike some of the other compounds, decarbonylation was not involved in the major pathway for the fragmentation of **a**. A peak at m/z 110 was usually small and not always observed. Peaks at m/z 55, 70 and 83 represent predominant fragments for these compounds.

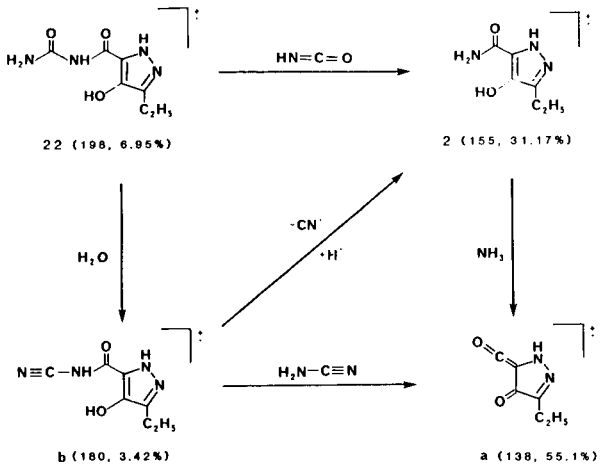
In contrast to the bicyclic pyrazolo[3,4-*e*][1,3]oxazines, a molecular ion for the related open-chain derivatives of **2** and **7** was usually lower in intenstiy and underwent at least a two step fragmentation to afford the basic fragment **a** (m/z 138). All of the analyzed *O*- and *N*-substituted derivatives of **2** and **7** showed a peak at m/z 155 (239) which corresponds to the carboxamide **2** which then underwent a regular fragmentation. The relative intensity of the peak



Scheme 10


THP
-DHP
(S)O
-(X=C=NH)
-(X=C=NH)
THP
-DHP
(S)O
a (m/z 222)
a (m/z 138 or 154)
(180; 34.5%)
a (138; 100%)
+ NH=C=NH
O=C=C=C=O
(68)
O=C=C=NH
(55)
CO
(70; 25.3%)
(83; 8.23%)
(110; 3.6%)
CO
(N2 + C3H6)
N≡C − C2H5
(55; 90%)
+ NH=C=C=O
(55)

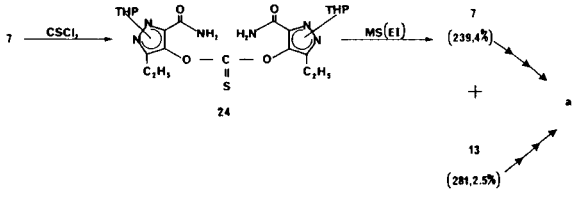
Scheme 11



Scheme 12

at m/z 155 (239) was variable. In some cases this intensity was less than 5% but sometimes would be as high as 48%. Therefore, the presence of the peak at m/z 155 (239) is very characteristic in the mass spectrum of the open-chain compounds and may be useful for a structure determination when the molecular ion is too small to be reliable and the fragment **b** gives the highest peak in the spectrum.

An excellent example of this is as follows: **7** with thiophosgene provided a product **24** which was isolated and showed a negative ferric chloride test and ms (EI) with the largest peak at m/z 281. This peak at m/z 281 is equal to the molecular ion peak of the bicyclic compound **13**, but the ms of **24** also revealed peaks at m/z 239 (**7**) and 155 (**2**) which, as it was mentioned above, could not be formed from **13**. This suggested an open-chain structure for **24** and the possibility of the structure illustrated in Scheme 13 in spite of the absence of a molecular ion peak at m/z 520. It would appear that **7** functions as a leaving group



Scheme 13

under electron impact conditions to furnish compound **13**. Compounds **7** and **13** then followed the fragmentation pathways described above to afford fragment **a** (Scheme 13). The ^{1}H nmr spectrum (broad doublet of NH_2 at 7.2 ppm), ir data and elemental analysis provided additional support for the structural assignment of **24**.

We are continuing research in this area and will be placing more emphasis in the synthesis of some monosubstituted derivatives.

In conclusion, we have found that with the use of certain precautions, the synthesis and chemical transformation of pyrazolo[3,4-*e*][1,3]oxazine derivatives is possible, and we are currently extending our work on this new ring system.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and were uncorrected. Elemental analysis (C,H,N) were determined by M-H-W Laboratories, Phoenix, AZ. Ultraviolet absorption spectra (uv) were obtained with a 8450A Hewlett-Packard spectrophotometer, and infrared spectra (ir) with a Perkin-Elmer 281 Infrared spectrometer. Nuclear magnetic resonance spectra were recorded with a Varian EM-360 spectrometer and a Bruker WM-360 spectrometer with chemical shift values reported in δ (ppm) relative to tetramethylsilane as an internal standard. Mass spectra (ms) were recorded by a Finnigan Model 4023 GC/MS (EI, 70 eV, direct insertion). ISCO lplc system was used for separations. Columns were Lobar^R, Li Chroprer^{TM} Si60 by Merck, and Michel-Miller's columns dry packed with silica gel 0.063-0.2 mm from Merck. For hpcl we used a Varian HPLC system which included a 5000 liquid chromatograph, UV-50 detector and chromatography data system 401 and with Micro Pak MCH-10, Magnum 9, and Partisil-10 columns by Whatman. Gravity column chromatography was performed by standard techniques on Merck's Silica gel 60. Thin-layer chromatography was performed on Analtech's 0.25 mm precoated plates and the substance were visualized with a short-wave (254 nm) uv light. All solvent proportions are given by volume. A rotor-evaporator and water-bath (about 40°) were used for the evaporations unless otherwise specified. All compounds were dried *in vacuo* (63°, 0.5 mm Hg) before submission for elemental analysis.

3-Ethylpyrazolo[3,4-*e*][1,3]oxazine-5,7-dione (**3**).

Method A.

Compound **2** (1.55 g, 10 mmoles) and 3.12 ml (22 mmoles) of triethylamine were added to 40 ml of dry dimethyl formamide. Ethyl chloroformate (1.92 ml , 20 mmoles) was then added dropwise to this stirred cold solution (−10 to −15°). The reaction mixture was allowed to warm up to room temperature and then gradually heated to reflux temperature. The mixture was heated at reflux for two hours, cooled to room temperature and the dimethyl formamide evaporated *in vacuo* at 40-45°. The resulting solid residue was washed with 10 ml of ice water, the precipitate was collected by filtration and crystallized from 9 ml of ethanol to yield 0.85 g (47%) of **3**, mp 217-220°. Recrystallization of the product with charcoal, furnished 0.03 g of **3** with mp 220.5-222°; uv λ max nm (ϵ) (*p*H 1): 323 (8,900), 269 (4,170); (*p*H 7): 232 (8,900), 269 (4,100); (*p*H 11): 242 (13,200), 265 sh (5,800); ir (potassium bromide): 3250, 3000-2900, 1760, 1625 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 13.95 (s, 1H, N_1-H); 11.88 (s, 1H, N_6-H), 2.76 (q, 2H, CH_2); ms: m/z 181 (M), 138, 109, 83, 70, 55.

Anal. Cacld. for $C7H_7N_3O_3$: C, 46.40; H, 3.87; N, 23.20. Found: C, 46.37; H, 4.06; N, 22.98.

Method B.

Compound **2** (0.155 g, 1 mmole) and *N,N'*-carbonyldiimidazole (0.17 g, 1.05 mmoles) were added to 7 ml of dry tetrahydrofuran under nitrogen and the reaction mixture was heated at reflux for 4.5 hours. A white precipitate was formed in approximately 15 minutes and then gradually redissolved. The solution was allowed to stand at 5° for 18 hours, the precipitate was collected by filtration, washed with 4 ml of ice cold water and dried *in vacuo* (63°, 0.5 mm Hg) to yield **3** (0.136 g, 75%). Recrystallization from ethanol gave a product with mp, uv, ^{1}H nmr and R_f values essentially identical to the product obtained by Method A.

Ethyl 1-(Tetrahydropyran-2-yl)-3(5)-ethyl-4-hydroxypyrazole-5(3)-carboxylate (**6**).

A solution of dihydropyran (DHP) (2.85 ml, 31.25 mmoles) in 5 ml of

ethyl acetate was added dropwise to a stirred solution of ethyl 5(3)-ethyl-4-hydroxypyrazole-3(5)-carboxylate (**1**, 5 g, 27.1 mmoles) and *p*-toluenesulfonic acid monohydrate (TsOH) (0.07 g, 0.368 mmole) in 45 ml of ethyl acetate at 50° over a period of 30 minutes. The mixture was then stirred at 55-60° for an additional 2 hours. The solution was chilled in an ice bath, and then treated with 3 ml of a 3*N* ammonium hydroxide solution. This solution was washed with water (4 × 40 ml) to neutral *p*H and the organic solution was dried over sodium sulfate for 4 hours. After evaporation of the ethyl acetate, 6.60 g of a residual oil was crystallized from hexane to afford 5.45 g of a white solid. Purification by column chromatography (chloroform) furnished 5.0 g (68% yield) of **6**, mp 62-67° as a mixture of two isomers.

Anal. Calcd. for $C_{13}H_{20}N_2O_4$: C, 58.41; H, 7.46; N, 10.45. Found: C, 57.96; H, 7.38; N, 10.36.

The isomeric mixture of **6** (3.0 g) was separated by column chromatography (2.5 × 40 cm, 60 g of silica gel, chloroform). Fractions 5-11 (50 ml each) were evaporated and 5 ml of hexane was added to the residual oil and the solvent was again removed by evaporation. The resulting oily residue was crystallized from 8 ml of hexane. A white solid was collected by filtration and dried *in vacuo* to afford the pure isomer **6a** (0.95 g). Fractions 17 and 18 were evaporated and after washing with hexane gave 0.1 g of pure **6b**. Intermediate fractions (12-16) were found to be a mixture of both isomers.

Compound **6a**.

This compound had mp 62-63°; R_f = 0.73; (chloroform:methanol/100:2/v:v); ^{1}H nmr (deuteriochloroform): δ 7.22 (s, 1H, OH); 5.87 (dd, 1H, $C_{2'}$-H, $J_{2',3'a}$ = 10.3 Hz, $J_{2',3'e}$ = 2.3 Hz), 4.44 (q, 2H, OCH_2), 4.13 (m, 1H, C_6-H*e*), 3.63 (m, 1H, C_6-H*a*), 2.66 (q, 2H, CH_2), 2.08 (m, 1H, C_3-H*a*), 1.90 (m, 1H, C_3-H*a*), 1.73-1.49 (m, 4H, C_4-H_2 and C_5-H_2), 1.43 (t, 3H, CH_3CH_2O), 1.25 (t, 3H, CH_3CH_2).

Compound **6b**.

This compound had mp 75-76°; R_f = 0.70; ^{1}H nmr: 7.02 (s, 1H, OH), 5.3 (dd, 1H, C_2-H, J_1 = 10 Hz, J_2 = 2.6 Hz), 4.43 (q, 2H, OCH_3), 4.05 (m, 1H, C_6-H*e*), 3.64 (m, 1H, C_6H*a*), Hz 2.73 (q, 2H, CH_2), 2.10 (m, 1H, C_3-H*e*), 1.90 (m, 1H, C_3-H*a*), 1.75-1.53 (m, 4H, C_4-H_2 and C_5-H_2), 1.41 (t, 3H, CH_3 CH_2O), 1.23 (t, 3H, CH_3CH_2).

1-(Tetrahydropyran-2-yl)-3(5)-ethyl-4-hydroxypyrazole-5(3)-carboxamide (**7**).

Method A.

Compound **6** (1.0 g, 37 mmoles) and 200 ml of liquid ammonia were heated in a sealed steel reaction vessel at 70-75° (oil bath) for 6 hour. The residue remaining after cooling and ammonia evaporation was then purified by column chromatography (4 × 60 cm, 200 g of silica gel, dichloromethane:methanol/970:30/v:v) to afford 6.86 g (77%) of a white solid, mp 134.5-136.5°; R_f by tlc 0.60 (chloroform:methanol/9:1/v:v); ms: m/z 239 (M), 155, 138, 85; ^{1}H nmr (deuteriochloroform): δ 7.8 (s, 1H, OH), 6.8-6.05 (br d, 2H, NH_2), 5.3 (dd, 1H, C_2-H), 4.3-3.3 (m, 2H, C_6-H), 2.8 (q, 2H, CH_2), 2.55-1.55 (m, 6H), 1.3 (t, 3H, CH_3).

Anal. Calcd. for $C_{11}H_{17}N_3O_3$: C, 55.23; H, 7.11; N, 17.57. Found: C, 55.25; H, 7.15; N, 17.57.

Method B.

A solution of DHP (1.17 ml 12.9 mmoles) in 10 ml of ethyl acetate was added dropwise to 1.0 g of **2** (6.45 mmoles) and 0.013 g of *p*-TsOH in 40 ml of ethyl acetate at 55° with stirring. The reaction mixture was stirred at 60-65° for 3 hours, then chilled in an ice bath and 6 ml of a 0.02 *N* solution of ammonium hydroxide was added to the mixture. The mixture was washed with water (4 × 10 ml) until the wash was at neutral *p*H. The ethyl acetate layer was dried over sodium sulfate and then evaporated to afford 1.04 g of **7** (68%). The mp of a sample crystallized from hexane:-chloroform (40:15) was 133-134.5°; R_f, ^{1}H nmr and ir were also identical to the sample obtained from Method A.

1(2)-Tetrahydropyran-2-yl)-3-ethylpyrazolo[3,4-*e*][1,3]oxazine-5,7-dione (**8**).

Compound **7** (0.120 g, 0.5 mmole) and *N,N'*-carbonyldiimidazole (0.085 g, 0.525 mmole) were added to 12 ml of dry toluene under a nitrogen atmosphere. The reaction mixture was heated at reflux for 100 minutes. The precipitate which had formed, after allowing the reaction mixture to stand at 0-5°, was collected by filtration and dried *in vacuo* (63°, 0.3 mm Hg). This compound, identical to **8b** prepared by the procedure below, was then redissolved in a mixture of 5 ml of 1 *N* ammonium hydroxide and 5 ml of water. The *p*H of the solution was adjusted to 6-7 by gradually adding an ion exchange resin (IR-120, H^+). The solid which had separated was collected by filtration and dried *in vacuo* to afford 0.065 g (~45%) of **8**, mp 184-187°. Recrystallization of **8** from a toluene/hexane mixture gave 20 mg of an analytically pure compound, mp 185.5-187°; ^{1}H nmr (DMSO-d_6): δ 11.8 (br s, 1H, N_6-H), 5.7-5.75 (dd, 1H, C_2-H).

Anal. Calcd. for $C_{12}H_{15}N_3O_4$: C, 54.34; H, 5.66; N, 15.85. Found: C, 54.31; H, 5.34; N, 15.68.

1-(Tetrahydropyran-2-yl)-3(5)-ethyl-4-(1-imidazolecarbonyloxy)pyrazole-5(3)-carboxamide (**8a**) and a Complex of Imidazole with 3-Ethylpyrazolo-[3,4-*e*][1,3]oxazine-5,7-dione (**8b**).

Compound **7** (0.3585 g, 1.5 mmoles) and *N,N'*-carbonyldiimidazole (0.28 g, 1.725 mmoles) were dissolved in 25 ml of dry tetrahydrofuran and then heated at reflux temperature under nitrogen for 5 hours. The white precipitate which had formed, after allowing the reaction mixture to stand at 0-5° for 18 hours, was collected by filtration to afford 0.3 g of **8a**; ir (potassium bromide): 3350, 3180, 3000-2900, 1800, 1695, 1630 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.45 (s, 1H, C_2-H), 7.75 (s, 1H, C_5~H), 7.15 (s, 1H, C~H), 7.50 and 7.28 (br d, 2H, $CONH_2$) plus the expected signals for the THP and ethyl group protons.

The compound **8a** (0.1 g) was dissolved in toluene and heated at reflux for 80 minutes. The solution was cooled to 5°, the white precipitate was collected by filtration, washed with 10 ml of hexane, dried *in vacuo* (0.5 mm Hg, 65°) to furnish 0.086 g of **8b**, mp 179-180°; R_f by tlc 0.73 (ethyl acetate); ^{1}H nmr (DMSO-d_6): δ 7.72 (s, 1H, C_2~H), 7.10 (s, 2H, $C_{4',5'}$~H).

Anal. Calcd. for $C_{15}H_{19}N_5O_4$: (**8b**) C, 54.05; H, 5.70; N, 21.02. Found: C, 53.96; H, 5.67; N, 21.00.

3(5)-Ethyl-4-hydroxypyrazole-5(3)-thiocarboxamide (**9**).

A mixture of **2** (3.1 g, 20 mmoles) and purified phosphorus pentasulfide [29] (5.0 g, 22.5 mmoles) was added to 175 ml of dry dioxane and the reaction mixture was heated at reflux for 4.5 hours. The reaction mixture was cooled and the precipitate which had separated was collected by filtration. The filtrate was evaporated *in vacuo* to afford a residual thick oil. This oil was dissolved in 150 ml of boiling 1*N* hydrochloric acid, charcoal was added, and the mixture was then filtered. The filtrate was concentrated *in vacuo* to a volume of approximately 5 ml and then cooled in an ice bath. The precipitate was collected by filtration and dried in a vacuum desiccator over phosphorus pentoxide at room temperature. Purification by column chromatography (2.5 × 40 cm, 50 g of silica, chloroform:methanol/96:4/v:v), gave the crude compound **9**. A second purification furnished the analytically pure crystalline product, 1,406 g (41%), mp 180.5-182°: R_f 0.27 by (chloroform:methanol/9.5:0/v:v); ^{1}H nmr (DMSO-d_6): 12.82 (br s, 1H, N_1-H), 9.66 and 9.2 (two br s, 3H, OH, NH_2), 1.2 (t, 3H, CH_3); ms: m/z 171 (M), 154, 139, 122, 87, 70, 56; ir (potassium bromide): 3420, 3330, 3150, 3080, 1660, 1610 cm^{-1}.

Anal. Calcd. for $C_6H_9N_3OS$: C, 42.11; H, 5.26; N, 24.56. Found: C, 42.29; H, 5.44; N, 24.63.

3-Ethylpyrazolo[3,4-*e*][1,3]oxazine-7-thione-5-one (**10**).

Compound **9** (0.17 g, 1 mmole) and CDI (0.178 g, 1.1 mmoles) were added to 50 ml of dry tetrahydrofuran and the solution was heated at reflux for 11 hours. The solution was evaporated *in vacuo*, triturated with 10 ml of hexane, and the green precipitate was collected by filtration and then dried *in vacuo*. Purification of this solid by column chromatography (1 × 40 cm, 13 g of silica gel, ethyl acetate:hexane/1:1/v:v) gave 0.120 g (61%) of **10**, mp 235-237°. A second purificaton by column chromatography furnished an analytical sample, mp 237-238° dec; R_f 0.67 by tlc (ethyl acetate:hexane/7:3/v:v); uv (*p*H 1): λ max, nm (ε) 259 (8340), 313

(11570); (*p*H 7): 259 (8520), 314 (12460); (*p*H 11): 227 (3420), 321 (13630), sh 300 (11100); (methanol): 260 (7660), 315 (12000); ir (potassium bromide): 3260, 3130, 2990, 2920, 1750, 1800, 1550 cm^{-1}; ^1H nmr (DMSO-d_6): δ 13.95 (br s, ~1H, N_1-H), 13.0 (br s, ^1H, N_6-H), 2.7 (q, CH_2 + solvent), 1.2 (t, 3H, CH_3); ms: m/z 197 (M), 154, 139, 71, 56.

Anal. Calcd. for $C_7H_7N_3O_2S$: C, 42.67; H, 3.56; N, 21.34. Found: C, 42.85; H, 3.79; N, 21.09.

1-(Tetrahydropyran-2-yl)-3(5)-ethyl-4-(1-imidazolylthiocarbonyloxy)-pyrazole-5(3)-carboxamide (**11**).

Compound **7** (0.17 g, 0.75 mmole) and 0.156 g (0.788 mmole) of *N,N'*-thiocarbonyldiimidazole (90% pure, by Aldrich) were added to 15 ml of dry tetrahydrofuran and the reaction mixture was heated at reflux under nitrogen for 6 hours. The mixture was cooled in an ice bath, the precipitate which had separated was collected by filtration, washed with hexane, dried *in vacuo* to afford 0.176 g (76%) of a white product, mp 175-177° dec. This product was used for the next reaction without further purification since it provided correct elemental analysis; ms: m/z 350 (M + 1), 265, 155, 138.

Anal. Calcd. for $C_{15}H_{19}N_5O_3S$: C, 51.58; H, 5.44; N, 20.06. Found: C, 51.77; H, 5.72; N, 20.06.

1-(Tetrahydropyran-2-yl)-3(5)-ethyl-4-hydroxy-5(3)-(*N*-methoxythiocarbonyl)carboxamido)pyrazole (**14**) and 1-(Tetrahydropyran-2-yl)pyrazolo-[3,4-*e*][1,3]oxazin-7-one-5-thione (**13**).

Method A.

Compound **11** (0.792 g, 2.269 mmoles) was added to 0.218 g (4.538 mmoles) of sodium hydride (as a 50% suspension oil) in 42 ml of dry glyme. The suspension was stirred and gradually warmed to gentle reflux under an nitrogen atmosphere. The mixture became clear after 1 hour and then a small amount of a new precipitate was formed. After 1.5 hours, the yellow mixture was cooled in an ice bath and 4 ml of methanol was added. The solution was evaporated to dryness *in vacuo* and the resulting residue was dissolved in 20 ml of water and 10 ml of methanol. An ion-exchange resin (Amberlite, IR-120, H^+) was gradually added in order to adjust the *p*H value to 5.5-6.0. The solid which had formed was dissolved by the slow addition of methanol, the solution was filtered and then evaporated *in vacuo* to yield a yellow solid. Separation of this mixture by lplc (Lobar, size B, methylene chloride) gave 0.1 g of **13** (16%, mp 157-158.5°) which was identical to that obtained by Method B (see below) and 0.06 g of **14** (8.5%, mp 165-167°); ^1H nmr (deuteriochloroform): δ 9.8 (br s, 1H, O-H), 7.1 (s, 1H, N-H), 5.2-5.4 (dd, 1H, C_2-H), 4.2 (s, 3H, OCH_3); ms: m/z 313 (M), 229, 138, 85; ir (film): 3420, 2282, 2940, 1720, 1525 cm^{-1}.

Anal. Calcd. for $C_{13}H_{19}N_3O_4S$: (**14**) C, 49.84; H, 6.07; N, 13.49. Found: C, 49.93; H, 6.01; N, 13.26.

Method B.

Compound **11** (0.698 g, 2 mmoles) and 0.064 g (2.6 mmoles) of solid sodium hydride were added, with magnetic stirring, to 50 ml of dry glyme under a nitrogen atmosphere. The suspension was heated at gentle reflux for 100 minutes and a yellow solution was gradually formed. This solution was filtered through glass wool under nitrogen and the filtrate was evaporated *in vacuo* to dryness. The yellow residue **12** was treated with 40 ml of chloroform and then with 30 ml of a saturated aqueous ammonium chloride solution. The aqueous layer was then separated and extracted with chloroform (4 × 10 ml). The combined extracts were washed with cold water until the washings did not show the presence of Cl^- (silver nitrate test, 4 × 10 ml), and then dried over magnesium sulfate. Evaporation *in vacuo* furnished a white foam-like residue (0.283 g) which solidified when triturated with 10 ml of hexane. A final purification by lplc (Lobar, size B, 1% methanol in chloroform) gave 0.19 g (34%) of **13**, mp 158-159°; R_f by tlc 0.68 (chloroform:methanol/9.5:0.5); uv (*p*H 1): λ max nm (ε) 232 (12300), 261 (21300), 300 (13500); (*p*H 7): 236 (12800), 264 (15700), 305 (13900); (*p*H 11): 240 (14100), 281 (14850), 314 (16360); (methanol): 232 (15560), 260 (21200), 300 (16900); ir (film): 3150 (br), 2940, 2860, 1760, 1610, 1470 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.28 (br s, ~1H, N-H), 5.46 (dd, 1H, C_2-H, $J_{2',3'a}$ = 8.6 H_z $J_{2',3'e}$ = 3.0 Hz), 3.93 (m, 1H, C_6-H*e*), 3.68 (m, 1H, C_6-H*a*), 2.88 (q, 2H, CH_2), 2.61 (s, 3H, CH_3S), 2.2 (m, 1H, C_3-H*e*), 2.05 (m, 1H, C_3-H*a*), 1.8-1.6 (m, 4H, C_4-H_2, C_5-H_2), 1.35 (t, 3H, CH_3); ms: m/z 281 (M), 222, 197, 139, 138, 85.

Anal. Calcd. for $C_{12}H_{15}N_3O_3S$: (**13**) C, 51.24; H, 5.34; N, 14.95. Found: C, 51.43; H, 5.46; N, 14.95.

3-Ethylpyrazolo[3,4-*e*][1,3]oxazin-7-one-5-thione (**15**).

Compound **13** (0.090 g, 0.32 mmole) was dissolved in 15 ml of dry methylene chloride and hydrogen chloride gas was passed through the solution for 1 minute at 5°. The reaction mixture was maintained at this temperature for an additional 30 minutes. A white precipitate was collected by filtration, washed with 10 ml of hexane, dried *in vacuo* at 60° for 18 hours to afford 0.05 g (86%) of **15**. An analytical sample was purified by column chromatography (1 × 25 cm, 5 g of silica gel, ethyl acetate) mp 223-224° dec; R_f by tlc (ethyl acetate) = 0.61; uv (*p*H 1): λ max nm 229 (7400), 261 (15700), 297 (8800); (*p*H 7): 230 (7800), 262 (13300), 299 (8500); (*p*H 11): 241 (11000), 273 (8700), 308 (10800); ir (potassium bromide): 3150 (br), 2920, 1745, 1615, 1460 cm^{-1}; ^1H nmr (DMSO-d_6): δ 14.1 (br s, ~1H), 13.25 (br s, ~1H, N_6-H), 2.6 (q, CH_2), 1.25 (t, 3H, CH_3); ms: m/z 197 (M), 138, 83, 70, 59, 55.

Anal. Calcd for $C_7H_7N_3O_2S$: C, 42.64; H, 3.55; N, 21.32. Found: C, 42.62; H, 3.60; N, 21.12.

1-(Tetrahydropyran-2-yl)-3-ethyl-5-methylthiopyrazolo[3,4-*e*][1,3]oxazin-7-one (**16**).

Compound **13** (1.50 g, 4.3 mmoles) and 0.134 g (5.58 mmoles) of solid sodium hydride were added with stirring to 100 ml of dry glyme under nitrogen. The mixture was heated at gentle reflux for 2 hours. The yellow solution was cooled in an ice bath and then filtered through glass wool under nitrogen into a new flask. Methyl iodide (0.54 ml, 8.6 mmoles) was then added to the cold solution of **12**. The mixture was allowed to stand in the sealed flask with stirring for 18 hours (2 hours in an ice bath, then at room temperature). The solution was evaporated *in vacuo* to afford an oil which was then dried *in vacuo* (room temperature, 0.3 mm Hg) for 2 hours. This thick oil was treated with 10 ml of ice cold water and 50 ml of chloroform. The chloroform solution was washed with cold water until there was a negative reaction observed for I^- (silver nitrate test) and then dried over sodium sulfate for 4 hours. The oily residue obtained after evaporation *in vacuo* was then dried at 40° and 0.3 mm Hg and the oil solidified (~1.1 g). Purification by column chromatography (2 × 40 cm, 50 g of silica gel, chloroform) gave 0.68 g of the analytically pure **16**, 54%, mp 161-163°; R_f by tlc (chloroform:methanol/9.5:0/v:v); uv (*p*H 1): λ max nm (ε) 205 (13700), 236 (10905); (*p*H 7): 239 (10620), 271 (17490); (*p*H 11): 253 (17800), sh 240; (methanol): 267 (17960); ir (film): 2940, 2860, 1708, 1603, 1553, 1500 cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.5 (dd, 1H, C_2-H), 2.6 (s, 3H, CH_3S); ms: m/z 296 $(MH)^+$, 222, 138, 85.

Anal. Calcd. for $C_{13}H_{17}N_3O_3S$: C, 52.88; H, 5.76; N, 14.24. Found: C, 52.77; H, 5.70; N, 14.08.

3-Ethyl-5-methylthiopyrazolo[3,4-*e*][1,3]oxazin-7-one (**17**).

Hydrogen chloride (gas) was passed through a stirred solution of **16** (0.1 g, 0.339 mmole) in 25 ml of dry methylene chloride for 1.5 minute at 4°. The reaction mixture was kept at the same temperature for an additional 30 minutes. A white precipitate was collected by filtration, washed with 10 ml of hexane and dried *in vacuo* (63°, 0.1 mm Hg) for 18 hours. The white solid (64 mg) was crystallized from 5 ml of ethyl acetate and furnished 26 mg (36%) of analytically pure **17**, mp 164-166° dec; R_f by tlc (chloroforom:ethyl acetate:methanol/8:2:0.5:0.7./v:v); uv (*p*H 1): λ max nm (ε) 209 (11200), 241 (11700); (*p*H 7): 236 (17900, 267 (18400); (*p*H 11); 243 (2900); 272 (1900); ir (potassium bromide): 3200 (br), 2980, 2930, 2860, 1705, 1600, 1540, 1590, 1480; ^1H nmr (DMSO-d_6): δ 11.7 (br s, N_7-H), 2.75 (q, 2H, CH_2), 2.60 (s, 3H, SCH_3), 1.25 (t, 3H, CH_3); ms: m/z 211 (M), 138, 110, 86, 83, 74, 70, 56.

Anal. Calcd. for $C_8H_9N_3O_2S$·0.25 H_2O: C, 44.45; H, 4.87; N, 19.49. Found: C, 44.26; H, 4.58; N, 19.16.

5-Amino-1-(tetrahydropyran-2-yl)-3-ethylpyrazolo[3,4-*e*][1,3]oxazin-7-one (**18**) and 3(5)-Ethyl-4-hydroxy-1-(tetrahydropyran-2-yl)-5(3)-*S*-methylisothioureidocarbonylpyrazole (**19**).

Method A.

Compound **16** (0.153 g, 0.52 mmole) was dissolved in 12 ml of dry methylene chloride. Ammonia gas was then passed through the solution for one hour while maintaining the temperature at 2°. The flask was then closed and stirring was continued an additional 6 hours at room temperature. The solvent was evaporated *in vacuo* and the residue was dried in a vacuo-dessicator for 18 hours. This furnished 0.15 g of a greenish solid which was purified by lplc (silica gel chloroform:methanol/95:5/v:v). The first pass through the column gave only crude **18** and **19**. A second pass using the same conditions as above furnished pure samples of **19** (0.06 g, 37%), mp 149-150° dec and **18** (0.052 g, 38%), mp >171 dec; R_f by tlc (chloroform:methanol/9:1/v:v) 0.61 (**19**) and 0.34 (**18**) (see Method B); ^1H nmr (**19**, deuteriochloroform): δ 10.1-9 (br ~2H, NH, OH), 5.3 (dd, 1H, C_2-H), 2.6 (s, SCH_3), plus signals for the protons of THP and ethyl protons; ms: m/z: 312 (M).

Anal. Calcd. for $C_{13}H_{20}N_4O_3S$: (**19**) C, 50.00; H, 6.41; N, 17.95. Found: C, 49.82; H, 6.22; N, 17.84.

Method B.

Compound **16** (0.564 g, 1.912 mmoles) and triethylamine (0.4 ml, 2.87 mmoles) were dissolved in 50 ml of dry methylene chloride and ammonia gas was passed through the solution for 2.5 hour at 10°. The flask was then sealed and the solution was stirred for an additional 4 hours at room temperature. The mixture was cooled in an ice bath and ammonia gas was passed through for 5 minutes. The mixture was then heated at reflux for 5 hours and allowed to stand at room temperature for 18 hours. A removal of the solvents *in vacuo* gave a greenish solid (~ 0.8 g). Separation of the mixture by column chromatography (2 × 40 cm, 60 g of silica gel, chloroform:methanol/95:5/v:v) furnished compound **18** (0.376 g) and **19** (0.163 g). Additional washing of **18** with 10 ml of hexane gave analytically pure **18** (0.325 g, 64%), mp 178-180 dec; R_f 0.34 by tlc (chloroform:methanol/9:1/v:v); uv (*p*H 1): λ max nm (ε) 210 (17000), 238 (11300); (*p*H 7): 220 (11200), 247 (15760); (*p*H 11): 247 (15800); (methanol): 247 (16700); ^1H nmr (DMSO-d_6): δ 7.8 (br s, 2H, NH_2), 5.6 (dd, 1H, C_2-H) plus the signals expected for THP and ethyl protons; ms: m/z 312 (M), 228.

Anal. Calcd. for $C_{12}H_{16}N_4O_3$: (**18**) C, 54.54; H, 6.06; N, 21.21. Found: C, 54.51; H, 6.11; N, 21.30.

1-(Tetrahydropyran-2-yl)-3(5)-ethyl-4-hydroxy-5(3)-(*N*,$^1N^2$-dimethylguanidinocarbonyl)pyrazole (**21**).

Methylamine (gas) was passed through a cold (5°) solution of **16** (0.150 g, 0.508 mmole) for 30 minutes. The solution was stirred for an additional 30 minutes at room temperature. The solution was evaporated *in vacuo* to furnish a white crystalline product, which was triturated with 20 ml of warm (50-60°) dichloroethane and then filtered. The dichloroethane solution was then evaporated *in vacuo* to give a slightly colored residue. This residue was crystallized from chloroform to give 0.082 g of a white product (mp 182-192°). This compound was purified by column chromatography (1 × 40 cm, 10 g of silica, chloroform:methanol/9.5:0.5/v:v) to afford analytically pure **21** (0.0425 g, 27%) mp 232-234°; R_f 0.21 by tlc (chloroform:methanol/9.5:0.5/v:v); ^1H nmr (deuteriochloroform): δ 5.4 (dd, 1H, C_2-H), 2.9-2.6 (br s, 8H, $2CH_3N$ + CH_2) plus the expected signals of THP and CH_3 protons; ms: m/z 309 (M), 225, 155, 138.

Anal. Calcd. for $C_{14}H_{25}N_5O_3$: C, 54.40; H, 7.44; N, 22.65. Found: C, 54.24; H, 7.47; N, 22.47.

3(5)-Ethyl-4-hydroxy-5(3)-ureidocarbonylpyrazole (**22**).

A cold hydrochloric acid solution (2 ml of concentrated hydrochloric acid:H_2O/10:5) was added to compound **18** (0.0907 g, 0.34 mmole) which had previously been dissolved in 12 ml of methanol. The mixture was stirred and cooled in an ice bath for 20 minutes, then stirred for an additional 4 hours at room temperature. Evaporation *in vacuo* gave a white solid which was triturated and then stirred with 5 ml of chloroform. The solid was collected by filtration to afford 57.1 mg of crude **22**. A white precipitate, (19.4 mg) presumably **22a**, was obtained from the chloroform solution; (^1H nmr DMSO-d_6): δ 11.7 (br s, N_1-H), 9.65 (br s, CONHCO), 3.7 (s, 3H, CH_3), 2.6 (CH_2 + DMSO), 1.2 (t, 3H, CH_3); hplc purification of **22** (Partisil M9. RP-18, methanol:water, 30:70/v:v) gave 15 mg of an analytical sample of **22** which was dried over phosphorus pentoxide *in vacuo* for 3 days, mp 212-215° dec started ⊕192°; R_f by tlc (chloroform:methanol/18:12/v:v) 0.43; (acetonitrile) 0.39; uv (*p*H 1): λ max nm (ε) 207 (9400), 234 (7800), 282 (3300); (*p*H 7): 236 (8000), 282 (2600); (*p*H 11): 248 (6800), 339 (5600); ir (potassium bromide): 3380, 3240-3160, 2980, 1695, 1673, 1590 cm^{-1}; ms: m/z 198 (M), 181, 155, 138.

Anal. Calcd. for $C_7H_{10}N_4O_3 \cdot 0.25\ H_2O$: C, 41.48; H, 5.18; N, 27.65. Found: C 41.73; H, 5.00; N, 27.00.

5-Amino-3-ethylpyrazolo[3,4-*e*][1,3]oxazin-7-one (**23**).

Hydrogen chloride (gas) was passed through a stirred solution of **18** (0.5 g, 1.89 mmoles) in 120 ml of dry methylene chloride for 5 minutes at 0°. Stirring was then continued for an additional 50 minutes at 0° and then 2 hour at room temperature. A constant stream of nitrogen was passed through the reaction mixture. The white precipitate (0.38 g) was collected by filtration, washed with 10 ml of hexane and dried *in vacuo*. The precipitate was dissolved in 25 ml of dimethyl formamide and 0.268 ml (1.93 mmoles) of triethylamine in 5 ml of dimethyl formamide was added dropwise to the stirred solution. After 10 minutes, the dimethyl formamide was removed by evaporation, the resulting solid residue was washed with 10 ml of ice water and dried *in vacuo* (63°, 0.3 mm Hg) over phosphorus pentoxide. Recrystallization of the solid from 40 ml of ethanol furnished 0.164 g (45%) of **23**, mp 260-261° (dec started at 253°); R_f 0.22 by tlc (chloroform:methanol/9.1); uv (*p*H 1): λ max nm (ε) 209 (16750), sh 233 (10000), sh 270 (4000); (*p*H 7): 209 (21900), 245 (14500), sh 275 (6100); (*p*H 11): 226 (500), 262 (0500), 262 (10500); ir (potassium bromide): 3300-3000 (br), 1665, 1610 (sh), 1545, 1415 cm^{-1}; ^1H nmr (DMSO-d_6): δ 13.6 (br s, ~1H, N^1-H), 8.1 (br s, ~2H, NH_2), 2.7 (q, 2H, CH_2), 1.23 (t, 3H, CH_3); ms: m/z 180 (M), 138, 110, 83, 70, 55.

Anal. Calcd. for $C_7H_8N_4O_2$: C, 46.67; H, 4.44; N, 31.11. Found: C, 46.56; H, 4.53; N, 30.79.

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