Synthesis of 6-Substituted-2,3-dihydro-1*H*-imidazo[1,5-*b*]pyrazoles[1]

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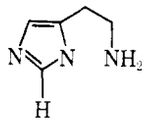
Received April 18, 1978

The synthesis of derivatives of 2,3-dihydroimidazo[1,5-*b*]pyrazole, a structurally novel heterocyclic system corresponding to cyclized histamine, is presented. It is based on the cyclodehydration of suitably substituted pyrazolylmethylacetamides, obtained by the catalytic hydrogenation of 3-cyano-4,5-dihydro-1*H*-pyrazoles. These latter precursors were conveniently obtained by the cycloaddition of acrylonitriles to diazomethane followed by in situ benzoylation to localize the double bond. All structures are thoroughly supported spectroscopically with the application of $Eu(fod)_3$ shift reagent where simplification was needed.

Histamine (**1**), a substance widely distributed in cellular systems, has long been known as a mediator of inflammation.[2] This physiological activity has initiated a search for various related structures that would act as partial or selective antagonists. This research has resulted in the introduction of various substituents in the imidazole nucleus[3] or in variations of the side chain;[4] more fundamental changes in the basic structure, however, have rarely been examined. For example, the closely related bicyclic compound **2** has not been reported. In this communication we describe the synthesis of this heterocyclic system substituted in the 6, 3 and 6, and 2 and 6 positions.



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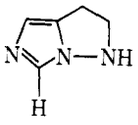

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The overall synthetic approach (Scheme I) utilized 3-cyanopyrazoline precursors, formed by the cycloaddition of diazomethane to substituted acrylonitriles.[5] We found it advantageous to treat the adducts with benzoyl chloride prior to isolation to prevent prototropic shifts.

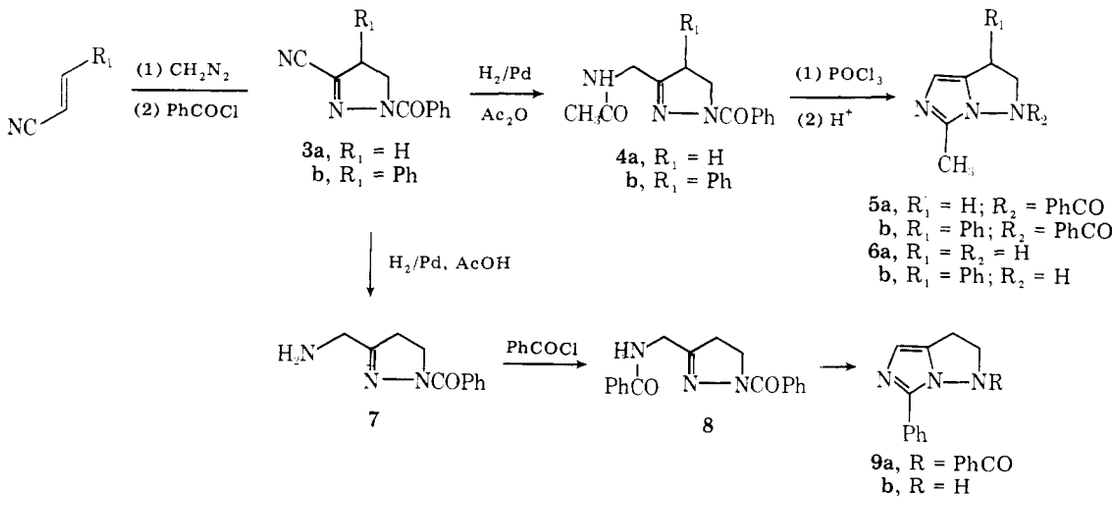
The crystalline benzoyl derivatives **3** were easily purified, and their structures were fully verified spectroscopically. The complicated ABM multiplet of the pyrazoline protons in the spectrum of **3b** was resolved into the component quartets by the addition of 12 mol % of $Eu(fod)_3$ shift reagent. Conversion of cyanopyrazolines **3** to the desired bicyclic structures **5** required the preparation of partially reduced intermediates **4**. Several catalysts (Raney Ni, PtO_2, and Pd/C) were found effective in reducing the cyano group without affecting the internal hydrazone. Palladium-catalyzed hydrogenations in acetic anhydride proved most effective and led to the isolation of acetylated derivatives **4a** and **4b**. An alternative procedure employing acetic acid as the solvent resulted in the isolation of the free amine **7** in quantitative yield, which could then be utilized for the introduction of other substituents into the 6 position of the final imidazo[1,5-*b*]pyrazole, as exemplified by the preparation of benzoyl derivative **8** and its cyclization.

Cyclic dehydration of intermediates **4** was readily achieved with $POCl_3$,[6] and the resultant benzoyl derivatives **5a, 5b,** and **9a** were converted to the desired **6a, 6b,** and **9b,** respectively, by acid hydrolysis.

The NMR spectrum of 2,3-dihydro-6-methyl-1*H*-imidazo[1,5-*b*]pyrazole (**6a**) fully confirms the assigned structure. The methyl group and lone imidazole proton give rise to singlets at 2.60 and 6.85 ppm, respectively. Protons of the dihydropyrazole ring appear as a set of multiplets; the triplet at 3.15 ppm is due to the methylene proximal to the imidazole nucleus, whereas the quartet at 4.00 ppm is due to the methylene α to the nitrogen. The assignment was substantiated by irradiating the signal of the nitrogen proton at 7.70 ppm and simultaneously collapsing the quartet at 4.00 ppm into a triplet. The multiplicity of the signal at 4.00 ppm is compatible only with a single proton on the pyrazoline nitrogen, thus designating the nonbridging nitrogen of the imidazole ring as the site of protonation in the HCl salt.

The NMR spectrum of derivative **6b** is more complicated. The additional phenyl substituent resulted in the generation of an ABM spectral system, which appears as a set of three multiplets at 3.68, 4.19, and 4.50 ppm. The former two quartets with coupling constants of 7 and 11 Hz belong to the methylene adjacent to the nitrogen; the proton at higher field

Scheme I



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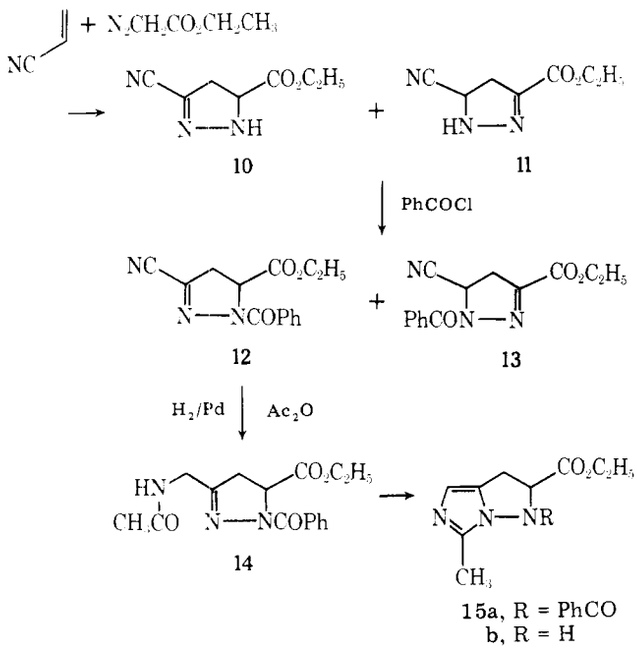
Scheme II



is in the shielding cone of the phenyl substituent. The latter triplet is generated by the benzylic methine proton and shows an identical coupling constant (7 Hz) with the protons of the vicinal methylene group. This assignment was supported by the use of shift reagent,[7] which caused a substantial downfield shift of the imidazole proton (8.57 ppm) and methyl protons (5.57 ppm), indicating that the site for complexation is the imidazole moiety. The methine triplet was shifted downfield by 0.67 ppm; this is substantially more than the multiplet due to the geminal protons, which are shifted 0.48 ppm downfield.

The successful synthesis of these bicyclic histamine analogues prompted us to undertake the preparation of the closely related histidine congeners. These compounds have not been reported previously, although a related *N*-oxide has been reported[8] from a reaction that neither others[9] nor we were able to repeat.

The chemistry is shown in Scheme II. Cycloaddition of ethyl diazoacetate to acrylonitrile[10] resulted in two isomeric compounds, the α,β-unsaturated nitrile **10** and the α,β-unsaturated ester **11** in solvent dependent ratios. Employing diethyl ether solvent, in which **11** is only partially soluble, the reaction afforded a 1:3 ratio of **10**/**11**, whereas in chloroform a reversal in the relative amounts of the respective tautomers was observed.

The two compounds were separated by chromatography, and their structures were verified spectroscopically. While the NMR spectra of **10** and **11** were virtually identical, their IR spectra allowed unambiguous assignment. The former compound displayed a very strong conjugated nitrile band at 2250 cm^{-1} and a strong band due to the unconjugated ester group at 1740 cm^{-1}. The IR spectrum of **11**, on the other hand, indicated an unconjugated nitrile group by the weak band at 2280 cm^{-1} and a conjugated ester by strong bands at 1700 and 1580 cm^{-1}. Treatment of the mixture of adducts in chloroform with benzoyl chloride afforded benzoyl derivatives **12** and **13** respectively, which were separated by chromatography. Structural assignment could be readily made from their IR spectra. The former displays a strong nitrile band at 2212 cm^{-1} in addition to the ethoxy carbonyl group at 1724 cm^{-1}, whereas **13** gives rise to a very weak nitrile band at 2222 cm^{-1} and it shows, in addition to the bathochromically shifted ethoxy carbonyl absorption at 1680 cm^{-1}, a C=N band at 1562 cm^{-1}.

Reduction of **12** to the acetamide **14** was an extremely facile process, carried out rapidly at ambient temperature. Conversion of **14** to the bicyclic structure **15a** was achieved by our previous procedure; however, the alkaline workup conditions led to saponification of both ethoxy carbonyl and benzoyl groups, affording an amino acid that was difficult to isolate. Isolation and purification of **15b** were finally accomplished by HCl/EtOH treatment of the crude cyclization product **15a**, resulting in the removal of the benzoyl group without saponification of the ester.

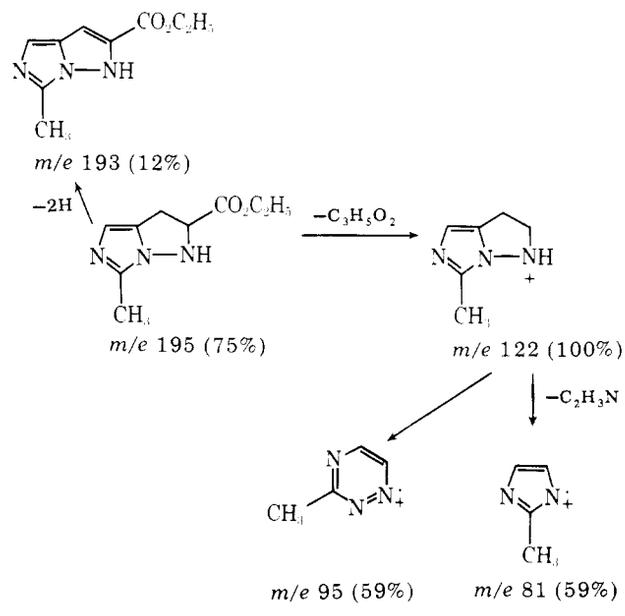
Proof of structure for **15b** is based firmly on its IR, NMR, and mass spectral behavior. The presence of the ethoxy carbonyl group is evidenced by a strong band at 1705 cm^{-1} and by the quartet–triplet combination at 4.55 and 1.50 ppm, respectively. Singlets for the imidazolyl and methyl protons are observed at 7.45 and 2.90 ppm, and the pyrazolyl protons give rise to an ABX multiplet at 5.40 and 3.80 ppm. The former one-proton methine quartet is strongly deshielded by the neighboring nitrogen atom and ethoxy carbonyl group. An analysis of the mass spectral fragmentation pattern of **15b** clearly demonstrates all of the structural features in the molecule, as shown in Scheme III. Pharmacological evaluation of **6a** in the PCA assay[11] indicated the absence of histamine blocking activity. Compound **6b** was tested in a dose range study employing Charles River rats and found to possess moderate amphetamine-like CNS stimulating activity.

Experimental Section

All melting points are uncorrected. NMR spectra were recorded on a Hitachi Perkin-Elmer R-24 spectrophotometer with the exception of the $Eu(fod)_3$ experiments, which were determined on a Perkin-Elmer R-32. Unless otherwise indicated, the NMR spectra were determined in ca. 0.01 M $CDCl_3$ solutions. IR spectra were taken on a Perkin-Elmer Infracord spectrophotometer in Nujol mulls. Mass spectra were determined using a Hitachi Perkin-Elmer RMN-6E spectrometer. The usual workup involved a chloroform extraction followed by washing the organic extract with brine, drying it over $MgSO_4$, and evaporating the filtrate at reduced pressure to obtain the product.

Cycloaddition Reactions with Diazomethane. Diazomethane, generated from 32.0 g of Diazald (Aldrich Chemical Co., Inc., Milwaukee, Wis.), was slowly added to an ice-cold solution of the appropriate acrylonitrile (0.12 mol) in 250 mL of ether with gentle stirring. The solvent was evaporated at reduced pressure, and the residual oil was taken up in 100 mL of ether and treated overnight with an ethereal solution of benzoyl chloride (11.6 g in 50 mL). The precipitate was filtered and purified by crystallization.

Scheme III



1-Benzoyl-3-cyano-4,5-dihydro-1*H*-pyrazole (3a) was crystallized from $CHCl_3$: mp 117–118 °C; IR 2220, 1650, 1170 cm^{-1}; NMR 8.1 and 7.8 (phenyl H), 4.35 and 3.1 (2t, J = 11 Hz, CH_2CH_2) ppm. Anal. Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.04; H, 4.63; N, 21.26.

1-Benzoyl-3-cyano-4,5-dihydro-4-phenyl-1*H*-pyrazole (3b) was purified by chromatography on SiO_2 and crystallized from MeOH: mp 93–95 °C; IR 2220, 1640, 1140 cm^{-1}; NMR 7.9 and 7.3 (phenyl H), 4.40 (m, CH_2CH_2) ppm; the multiplet was resolved into an ABX pattern at 6.65, 6.20, and 4.88 ppm with the addition of 5% $Eu(fod)_3$. Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 74.01; H, 5.05; N, 15.51.

Catalytic Hydrogenations. The nitrile (25 mmol) was dissolved in 250 mL of solvent, and Pd/C (5%, 2.0 g) was added. Hydrogenations were carried out in a Parr shaker at temperatures specified for each compound. When uptake of hydrogen was no longer evident, the reduction was discontinued and the solution was flushed with N_2 thoroughly before the catalyst was filtered. Removal of the solvent at reduced pressure yielded the products, which were purified by crystallization.

***N*-[(1-Benzoyl-4,5-dihydro-1*H*-pyrazol-3-yl)methyl]acetamide (4a).** Hydrogenation of **3a** in acetic anhydride at 55 °C yielded **4a** in 75% yield crystallized from ether: mp 135–135 °C; IR 3333, 1667, 1613 cm^{-1}; NMR 7.7 and 7.3 (phenyl H), 6.4 (brd, NH), 4.14 (s, $NHCH_2$), 4.04 (t, J = 8.0 Hz, NCH_2), 2.74 (t, J = 8.0 Hz, NCH_2CH_2), 1.97 (s, $COCH_3$) ppm. Anal. Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.33; H, 6.11; N, 17.07.

***N*-[(1-Benzoyl-4,5-dihydro-4-phenyl-1*H*-pyrazol-3-yl)-methyl]acetamide (4b).** Conversion of **3b** to **4b** was carried out in acetic anhydride at 55 °C, and the product was purified by EtOAc crystallization: mp 111–114 °C; IR 3279, 1667, 1600, 1563 cm^{-1}; NMR 7.75 and 7.25 (phenyl H), 6.23 (t, NH), 4.4–3.8 (m and s, 5 H), 1.8 (s, CH_3) ppm. Anal. Calcd for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.07. Found: C, 71.29; H, 6.09; N, 13.28.

3-Aminomethyl-1-benzoyl-4,5-dihydro-1H-pyrazole (7). Hydrogenation of **3a** in acetic acid at ambient temperature resulted in **7** in quantitative yield. The compound was purified by bulb-to-bulb distillation at 140–150 °C (0.1 mmHg): IR 3333, 1625, 1562 cm^{-1}; NMR 7.8 and 7.4 (phenyl H), 4.1 and 2.85 (t, J = 10 Hz, CH_2CH_2), 3.05 (s, CH_2), 1.6 (s, NH_2, exchanged by D_2O) ppm.

Cyclodehydrations. The amidopyrazole (30 mmol) was stirred overnight in 150 mL of $POCl_3$ at ambient temperature. Excess $POCl_3$ was removed by distillation, and 5% Na_2CO_3 solution was added to the residue. The aqueous solution was adjusted to pH 11 with 2.5 N NaOH and was worked up in the usual way. The products were crystallized as hydrochloride salts from 2-PrOH.

1-Benzoyl-2,3-dihydro-6-methyl-1*H*-imidazo[1,5-*b*]pyrazole (5a) was obtained from **4a** in 65% yield: mp 122 °C, IR 2632, 1695 cm^{-1}; NMR 7.9–7.5 (phenyl H), 7.2 (s, =CH), 4.7 (t, J = 7.0 Hz, NCH_2), 3.3 (t, J = 7.0 Hz, $=CCH_2$), 2.7 (s, CH_3) ppm. Anal. Calcd for $C_{13}H_{13}N_3O$·HCl: C, 59.20; H, 5.35; N, 15.93. Found: C, 58.89; H, 5.33; N, 16.12.

1-Benzoyl-2,3-dihydro-6-methyl-3-phenyl-1*H*-imidazo-[1,5-*b*]pyrazole (5b) was obtained from **4b** in 74% yield: mp 199–202 °C; IR 2500, 1667 cm^{-1}; NMR 7.95 and 7.55 (phenyl H), 7.60 (s, =CH), 5.3 (AB m, CH_2N), 4.65 (Hx, J = 10 and 12 Hz, CH), 2.85 (s, CH_3) ppm. Anal. Calcd for $C_{19}H_{17}N_3O$·HCl·0.25H_2O: C, 66.27; H, 5.42; N, 12.20. Found: C, 66.24; H, 5.37; N, 12.24.

1-Benzoyl-2,3-dihydro-6-phenyl-1*H*-imidazo[1,5-*b*]pyrazole (9a). The precursor amine **7** (2.8 g, 13.7 mmol) was dissolved in 50 mL of chloroform and mixed with 1.9 mL of triethylamine. The solution was cooled, and benzoyl chloride (1.9 g, 13.8 mmol) was added dropwise in a chloroform solution. The reaction was stirred at ambient temperature for 2 h and thoroughly washed with 2 N HCl, 5% Na_2CO_3 solution, and brine. The solution was dried over $MgSO_4$ and evaporated to a residual crude oil which was dissolved in a solution of 15 mL of $POCl_3$ in 250 mL of benzene and refluxed for 5 h. Usual workup yielded a solid (25% yield) crystallized from chloroform–ether: mp 180–181 °C; IR 1670 cm^{-1}; NMR 7.7, 7.45, and 7.2 (phenyl H), 6.75 (s, =CH), 4.52 (t, J = 7.0 Hz, $-NCH_2-$), 2.83 (t, J = 7.0 Hz, $=CCH_2$) ppm.

Acid-Catalyzed Hydrolysis. The benzoyl compounds (8 mmol) were dissolved in a solution of 15 mL of 12 N HCl in 300 mL of ethanol and refluxed overnight. Evaporation of the solution at reduced pressure afforded oily residues which were basified with 2.5 N NaOH and worked up in the usual manner.

2,3-Dihydro-6-methyl-1*H*-imidazo[1,5-*b*]pyrazole (6a) was obtained in quantitative yield and was crystallized as the HCl salt from ether and sublimed: mp 122 °C; IR 3571, 1626 cm^{-1}; NMR 10.26 (brd s NH^+), 7.7 (t, J = 8.0 Hz, NH), 6.85 (s, =CH), 4.0 (q, J = 7.0 Hz, NCH_2), 3.15 (t, J = 7.0 Hz, CH_2CH_2), 2.63 (s, CH_3) ppm. Anal. Calcd for $C_6H_9N_3$·HCl·0.5H_2O: C, 42.71; H, 6.57; N, 24.9. Found: C, 42.89; H, 6.39; N, 24.68.

2,3-Dihydro-6-methyl-3-phenyl-1*H*-imidazo[1,5-*b*]pyrazole (6b) was formed in 74% yield and was crystallized from ethyl acetate: mp 115–117 °C; IR 3125 cm^{-1}; NMR 7.28 (phenyl H), 6.55 (s, =CH), 4.50 (t, J = 7.0 Hz, Hx), 4.19 (q, J = 7.0 and 11.0 Hz, H_A), 3.68 (q, J = 7.0 and 11.0 Hz, H_B), 2.30 (s, CH_3) ppm. Anal. Calcd for $C_{12}H_{13}N_3$: C, 72.34; H, 6.58; N, 21.09. Found: C, 72.07; H, 6.67; N, 21.12.

Cycloaddition of Ethyl Diazoacetate to Acrylonitrile. To a solution of acrylonitrile (11.1 g, 0.21 mol) in 100 mL of ether was added ethyl diazoacetate (22.8 g, 0.2 mol) in 50 mL of ether dropwise over a period of 40 min. The cycloaddition was allowed to proceed for 72 h at ambient temperature, and the crystalline tautomer **11** (13.5 g) was filtered. The ethereal solution was placed on a SiO_2 "Dry Column" and was eluted with a 1:1 mixture of ether–cyclohexanol. The liquid tautomer **10** was eluted first (10.5 g) followed by some additional (4.1 g) solid **11**. Compound **10**: IR 3370, 2250, 1740 cm^{-1}; NMR 7.1 (s, NH), 4.5 (t, J = 10 Hz, CH), 4.2 (q, J = 7.0 Hz, OCH_2), 3.15 (d, J = 10 Hz, CH_2), 1.3 (t, J = 7 Hz, CH_2CH_3) ppm. Compound **11**: 3350, 2280, 1700, 1580 cm^{-1}; NMR 7.15 (s, NH), 4.7 (t, J = 9.0 Hz, CH), 4.35 (q, J = 8.0 Hz, OCH_2), 3.3 (d, J = 9 Hz, CH_2), 1.35 (t, J = 8.0 Hz, CH_3) ppm.

Benzoylation of Isomeric Mixture 10 and 11. The cycloaddition reaction was carried out in chloroform and in the manner above. Benzoyl chloride (33 g, 0.2 mol) in 200 mL of chloroform was added after 24 h, and stirring was continued for an additional 24 h. An equivalent quantity of triethylamine (20.2 g, 0.2 mol) was added to the reaction, and the organic solution was washed with H_2O and evaporated at reduced pressure. The benzoylated tautomers were chromatographed on a SiO_2 "Dry Column" using ether–cyclohexanol eluent. Product **12** (9.2 g) crystallized from the second fraction and was recrystallized from ether, mp 69–71 °C. The compound was identical with the derivative obtained by direct benzoylation of **10** using benzoyl chloride: IR 2220, 1750, 1630 cm^{-1}; NMR 7.85 and 7.5 (phenyl H), 5.15 (Hx, J = 8.0 and 12.0 Hz, CH), 4.25 (q, J = 7.0 Hz, OCH_2), 3.30 (AB, CH_2), 1.27 (t, J = 7.0 Hz, OCH_2CH_3) ppm. Anal. Calcd for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 62.20; H, 4.88; N, 15.63.

Isomer **13** was isolated from the fourth fraction (5.3 g) and was crystallized from EtOAc–cyclohexane, mp 99–100 °C. The product was identical with the benzoyl derivative obtained from **11** by direct benzoylation: IR 2230, 1710, 1650 cm^{-1}; NMR 8.0 and 7.55 (phenyl H), 5.45 (t, J = 9.0 Hz, CH), 4.35 (q, J = 7.0 Hz, OCH_2), 3.45 (d, J = 9.0 Hz, CH_2), 1.30 (t, J = 7.0 Hz, CH_2CH_3) ppm. Anal. Calcd for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 62.35; H, 5.11; N, 15.68.

Catalytic Hydrogenation of 12 (14). The crystalline nitrile **12** (6.7 g, 25 mmol) was dissolved in 25 mL of acetic anhydride, and Pd/C (5%, 2.0 g) was added. Hydrogenation was carried out in a Parr shaker at room temperature for 0.5 h. The solution was flushed with N_2, the catalyst was filtered, and the solvent was removed at reduced pressure. The resulting acetamide **14** was crystallized from EtOAc: mp 145–146 °C (66%); IR 3225, 1724, 1652, 1640 cm^{-1}; NMR 7.9–7.4 (phenyl H), 6.45 (brd, t, J = 6.0 Hz, NHCO), 5.0 (q, J = 7.0 and 12.0 Hz, CH), 4.2 (q, J = 7.0 Hz, OCH_2), 4.07 (d, J = 6.0 Hz, CH_2N), 3.5–2.5 (m, CH_2CH), 1.92 (s, $COCH_3$), 1.25 (t, J = 7.0 Hz, CH_2CH_3) ppm. Anal. Calcd for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.43; H, 6.02; N, 13.19.

Ethyl 2,3-Dihydro-6-methyl-1*H*-imidazo[1,5-*b*]pyrazole-2-carboxylate (15b). Acetamide **14** (5.0 g, 20 mmol) was stirred in 100 mL of $POCl_3$ overnight. The excess $POCl_3$ was removed at reduced pressure, and the residual crude **15a** (4.0 g) was taken up in 100 mL of ethanol acidified with gaseous HCl. The solution was stirred at ambient temperature for 72 h and the solvent removed at reduced pressure. The residue was washed several times with ether; even though TLC at this point indicated the presence of a single component, it could not be induced to crystallize either as the HCl salt or as the free base: *m/e* 195 (M^+), 193 (P − 2H), 122 (P − $C_3H_5O_2$), 95, 81; IR 3300, 1705 cm^{-1}; NMR (H_2O standard at 5.0 ppm, HCl salt) 7.45 (s, =CH), 5.40 (Hx, CH), 4.55 (q, J = 7.0 Hz, OCH_2), 3.80 (H_AH_B, m, CH_2), 2.90 (s, CH_3), 1.5 (t, J = 7 Hz, OCH_2CH_3) ppm.

Acknowledgment. The authors are indebted to our Analytical and Physical Chemistry Section personnel for analytical and physical data: Miss Edith Reich for elemental analyses; Dr. Edward White and Mr. Gerald Roberts for mass spectra; and Mr. David Staiger and Mr. John Simolike for the $Eu(fod)_3$ spectra.

Registry No.—**3a**, 67872-68-8; **3b**, 67862-69-9; **4a**, 67872-70-2; **4b**, 67872-71-3; **5a** HCl, 67872-72-4; **5b** HCl, 67872-73-5; **6a** HCl,

67872-74-6; **6b**, 67872-75-7; **7**, 67872-76-8; **9a**, 67872-77-9; **10**, 64847-17-2; **11**, 67872-78-0; **12**, 67872-79-1; **13**, 67872-80-4; **14**, 67872-81-5; **15a**, 67872-82-6; **15b** HCl, 67872-83-7; acrylonitrile, 107-13-1; 3-phenylacrylonitrile, 4360-47-8; diazomethane, 334-88-3; benzoyl chloride; 98-88-4; ethyl diazoacetate, 623-73-4.

References and Notes

(1) Presented in part at the 175th National Meeting Of the American Chemical Society, Anaheim, Calif., March 1978, Organic Division No. 65.
(2) M. A. Beaven, *N. Engl. J. Med.*, **294**, 30 (1976).
(3) (a) P. Dziuron, *Eur. J. Med. Chem. Chim. Ther.*, **10**, 129 (1975), and references cited; (b) K. Hofmann in "Imidazole and Its Derivatives", Part 1, A. Weissberger, Ed., Interscience, New York, N.Y., 1953, p 158.
(4) G. J. Durant, J. C. Emmett, C. R. Ganellin, A. M. Roe, and R. A. Slater, *J. Med. Chem.*, **19**, 923 (1976), and references cited.
(5) K. Von Auwers and O. Ungemach, *Chem. Ber.*, **66**, 1201 (1933); D. Gotkins and J. B. Cloke, *J. Am. Chem. Soc.*, **56**, 2710 (1934); R. Huisgen, R. Grashey, and J. Sauer in "The Chemistry of Alkenes", S. Patai, Ed., Interscience, London, 1964, Chapter 11.
(6) E. Abushanab, A. P. Bindra, L. Goodmann, and H. Peterson, Jr., *J. Org. Chem.*, **38**, 2049 (1973).
(7) B. C. Mayo, *Chem. Soc. Rev.*, **2**, 49, (1973).
(8) H. V. Euler and H. Hasselquist, *Arkiv. Kemi*, **13**, 185 (1958).
(9) H. C.Wormser and W. H. Chiu, *J. Heterocycl. Chem.*, **12**, 595 (1975).
(10) J. M. Gurvich and A. D. Teremtév, *Obshch. Khim. Akad. Nauk USSR*, 409 (1973).
(11) J. Goose and A. M. J. N. Blair, *Immunology*, **16**, 749 (1959).

Pyrimido[4,5-*c*]pyridazines. 1. Cyclizations with α-Keto Esters

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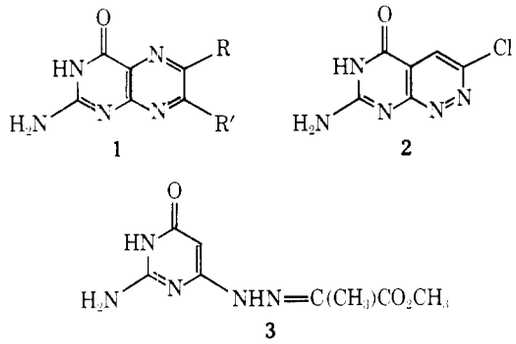
Received April 28, 1978

6-(1-Alkylhydrazino)isocytosines cyclize with simple α-keto esters to give pyrimido[4,5-*c*]pyridazine-4,5(1*H*,6*H*)-diones. The ease of cyclization for analogous 2-amino-6-(1-alkylhydrazino)pyrimidines varies with the nature of the functional group at position 4. Diethyl ketomalonate cyclizes in an unexpected manner with 6-(1-methylhydrazino)isocytosine to give the 3,5(1*H*,2*H*)-dione **11a**, whereas cyclization with 2,4-diamino-6-(1-methylhydrazino)pyrimidine occurs predictably to give the 4(1*H*)-one **12**.

Our search for analogues of the naturally occurring pterins (**1**)[1] has led to the synthesis of pyrimido[4,5-*c*]pyridazines. Few syntheses of this ring system have been reported,[2] and only one example (**2**) resembles the pterins in the pyrimidine portion of the molecule.[2c]

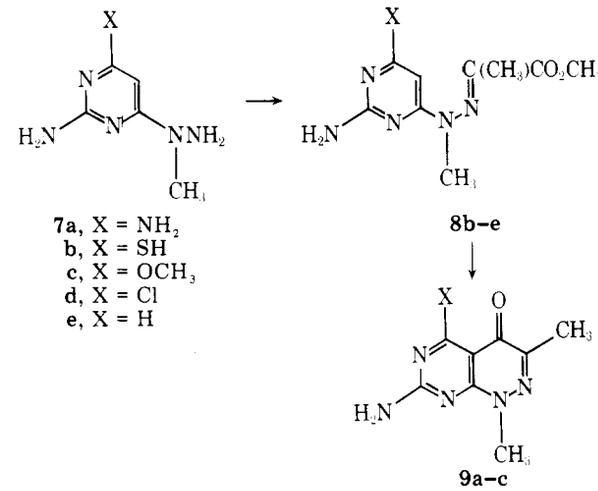
Pfleiderer reported[3] that the hydrazone formed from 1,3-dimethyl-6-hydrazinouracil and methyl pyruvate showed no tendency to cyclize, and we have noted the same behavior with the hydrazone (**3**) formed from methyl pyruvate and 6-hydrazinoisocytosine.[4] In contrast, we have found that 6-(1-*alkyl*hydrazino)isocytosines (**4**) readily form cyclic products (**6**) with a variety of α-keto esters (**5**; Table I). The isomeric pyrimido[4,5-*c*]pyridazine-3,5(1*H*,2*H*)-dione structure was ruled out because of characteristic mass spectral losses of R^2CN from representative molecular ions of these products, while the absence of pyrimidine C-5 protons in the NMR spectra removed the isomeric pyrimido[6,1-*c*]-*as*-triazine structure (and less likely structures which would involve cyclization across the 2-amino group and a ring nitrogen) from consideration.



1 **2**

3

The effect on ring closure of the substituent at position 4 of the pyrimidine ring was examined with a group of 6-(1-methylhydrazino)pyrimidines (**7**) prepared by treatment of the appropriate 6-chloropyrimidines with methylhydrazine. The one exception was the 4-methoxy compound (**7c**), which was prepared by treatment of the 4-chloro compound (**7d**) with methanolic sodium methoxide in a bomb. When these intermediates were allowed to react with methyl pyruvate, substantial differences in behavior were observed. In a qualitative sense, the ease of cyclization paralleled the degree of activation by substituents in electrophilic substitution reactions; cyclization to **9** occurred most readily with the 4-amino substituent (no hydrazone intermediate **8** being isolated), while no conditions could be found for cyclization of the intermediates formed from the 4-chloro or 4-unsubstituted compounds (**8d** and **8e**, respectively).



7a, X = NH_2
b, X = SH
c, X = OCH_3
d, X = Cl
e, X = H

8b–e

9a–c

Hydrazone **8d** did produce pyrimidopyridazine **10** in low yield when heated for 6 days in *n*-propanol, although this same product was produced in better yield by the reaction of hydrazone **8d** with hydrazine **7d**. These results suggest that in the former case the cyclization to **10** may have occurred after a slow solvolysis of **8d** back to **7d**, followed by further reaction with **8d**, thus providing an activating group at pyrimidine position 4 which would then allow the cyclization to proceed.

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