Recrystallization from carbon tetrachloride gave 10.2 g (65%) of **6** as a white, crystalline solid, mp 96–97 °C.

Anal. Calcd for $C_{12}H_{14}N_4O_3$: C, 54.96; H, 5.38; N, 21.36. Found: C, 54.88; H, 5.45; N, 21.36.

The material insoluble in carbon tetrachloride was removed by filtration and recrystallized from ethanol/acetonitrile to give 1.0 g of the dialkylated product (**7**), mp 237–238 °C.

Anal. Calcd for $C_{18}H_{18}N_8O_3$: C, 54.82; H, 4.60; N, 28.41. Found: C, 54.84; H, 4.63; N, 28.24.

2-Amino-3-cyano-5-phthalimidomethylpyrazine (10). A mixture of 2.69 g (12.6 mmol) of **1**, 2.6 g (14 mmol) of potassium phthalimide, and 35 ml of DMF was stirred at room temperature for 30 min. There was an initial mild exothermic reaction with the temperature rising from 18 to 33 °C. The mixture was poured into 50 ml of water and the resulting precipitate collected by filtration, dried, and recrystallized from 350 ml of acetonitrile to give 3.2 g (91%) of a white, crystalline solid, mp 275–276 °C dec.

Anal. Calcd for $C_{14}H_9N_5O_2$: C, 60.21; H, 3.25; N, 25.08. Found: C, 60.58; H, 3.36; N, 24.94.

2-Amino-3-cyano-5-(2-carboethoxyethyl)pyrazine (19). A mixture of 0.58 g (2.0 mmol) of **4**, 0.15 g (2.5 mmol) of sodium chloride, 0.15 ml (8.0 mmol) of water, and 15 ml of Me_2SO was placed in a three-necked 50-ml round-bottomed flask fitted with a thermometer, condenser, and magnetic stirrer. Attached to the condenser was a trap containing a solution of saturated barium hydroxide which was used to monitor CO_2 evolution. The mixture was heated at 155–170 °C for 6 h, cooled, and poured into 50 ml of water. The aqueous solution was extracted five times with 15-ml portions of chloroform. The combined chloroform extracts were dried (Na_2SO_4), filtered, and evaporated to give an oil which solidified upon drying in vacuo for 4 h. Recrystallization from carbon tetrachloride (charcoal) gave 0.34 g (77%) of **19** as a white, crystalline solid, mp 85–86 °C.

Anal. Calcd for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44. Found: C, 53.98; H, 5.29; N, 25.14.

1-(2-Amino-3-cyano-5-pyrazinyl)-3-butanone (13). Using the same procedure as outlined above for the preparation of **19**, 10.2 g (0.039 mol) of the keto ester **6** was decarboethoxylated to give 5.3 g (72%) of **13** as a white, crystalline solid, mp 130–131 °C after recrystallization from benzene.

Anal. Calcd for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.98; H, 5.38; N, 29.02.

1-(2-Amino-3-cyano-5-pyrazinyl)-2-carboethoxy-4-ethoxy-3-butanone (8). A solution of the sodium salt of ethyl γ-ethoxyacetoacetate was prepared by adding 0.48 g (10 mmol) of a 50% NaH–paraffin oil dispersion to 25 ml of freshly distilled dry THF followed by addition, under nitrogen at 5 °C, of a solution of 1.74 g (10 mmol) of ethyl γ-ethoxyacetoacetate in 10 ml of dry THF. The mixture was stirred at room temperature for 1 h and then added dropwise to a solution of 2.13 g (10 mmol) of **1** in 25 ml of dry THF at room temperature under nitrogen. This mixture was stirred for 4 h, poured into 50 ml of saturated sodium chloride solution, neutralized with 6 N HCl, and then extracted three times with 40-ml portions of chloroform. The combined chloroform extracts were dried (Na_2SO_4), filtered, and evaporated to give an oil. Trituration with benzene resulted in a separation of a solid which was collected by filtration, dried, and recrystallized from 2-propanol to give 0.60 g (20%) of a white solid, mp 194–195 °C, which appeared from microanalytical data and spectral analysis to be the dialkylated product **9**.

Anal. Calcd for $C_{20}H_{22}N_8O_4$: C, 54.79; H, 5.06; N, 25.56. Found: C, 54.80; H, 5.28; N, 25.51.

Evaporation of the benzene filtrates then gave 2.1 g (70%) of **8** as an oil: NMR ($CDCl_3$) δ 8.18 (s, 1), 5.65 (b, 2), 4.5–3.2 (m, 9), 1.25 (t, 6); IR (neat) 1750 (ester), 1725 (ketone), 2225 (CN), 3250–3450 cm^{-1} (NH_2).

1-(2-Amino-3-cyano-5-pyrazinyl)-4-ethoxy-3-butanone (21). A mixture of 2.1 g (7 mmol) of the keto ester **8**, 0.58 g (10 mmol) of sodium chloride, 0.5 ml of water, and 20 ml of Me_2SO was placed in a 50-ml three-necked round-bottomed flask fitted with a thermometer, condenser, and magnetic stirring bar. The mixture was heated at 150–160 °C for 5 h, cooled, and poured into 100 ml of water. Some black, polymeric material precipitated which was removed by filtration. The aqueous filtrate was then extracted four times with 50-ml portions of chloroform and the combined chloroform extracts dried (Na_2SO_4), filtered, and evaporated. The residual oil crystallized upon trituration with hexane and cooling. Recrystallization from carbon tetrachloride gave 0.30 g (19%) of **21** as a white, crystalline solid, mp 89–91 °C.

Anal. Calcd for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.28; H, 5.89; N, 24.18.

1,3-Bis(2-amino-3-cyano-5-pyrazinyl)-2-cyano-2-carbomethoxypropane (11). A solution of the sodium salt of methyl cyanoacetate was prepared by adding 1.62 g (15.7 mmol) of 97% methyl cyanoacetate in 15 ml of dry THF to a stirred mixture of 0.75 g (15.7 mmol) of 50% NaH–paraffin oil dispersion in 15 ml of THF under nitrogen at 0 °C. After stirring at room temperature for 30 min, this mixture was added to a stirred solution of 3.20 g (15 mmol) of **1** in 30 ml of dry THF at room temperature under nitrogen. The mixture was stirred at room temperature for 4 h, poured into 100 ml of saturated sodium chloride solution, neutralized with 10% HCl, and then extracted with 100 ml of chloroform. The chloroform extracts were dried (Na_2SO_4), filtered, and evaporated to give a crude solid which was partially purified by extraction with hot benzene. The benzene-insoluble material was further purified by dissolving in 60 ml of boiling acetonitrile, decolorizing with charcoal, and then concentrating to a small volume followed by cooling. This gave 1.9 g (67%) of **11** as a yellow solid, mp 213–215 °C dec.

Anal. Calcd for $C_{16}H_{13}N_9O_2$: C, 52.89; H, 3.61; N, 34.70. Found: C, 52.54; H, 3.92; N, 34.79.

1-(2-Amino-3-cyano-5-pyrazinyl)-3-ethylenedioxybutane (14). A mixture of 1.90 g (10 mmol) of **13**, 0.93 g (15 mmol) of ethylene glycol, 50 mg of *p*-toluenesulfonic acid, and 40 ml of benzene was placed in a 100-ml round-bottomed flask fitted with a Dean-Stark trap and condenser, and heated under reflux for 8 h. The reaction mixture was decanted while hot to remove some insoluble tarry material and poured into an equal volume of hexane. Cooling resulted in the separation of yellow needles which were collected by filtration, dried in vacuo, and recrystallized from benzene/cyclohexane to give 1.90 g (82%) of **14**, mp 126–127 °C.

Anal. Calcd for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.59; H, 6.20; N, 24.87.

1-(2,4-Diamino-6-pteridinyl)-3-ethylenedioxybutane (15). To a solution of sodium methoxide [from 0.55 g (24 mmol) of sodium in 30 ml of dry methanol] was added 1.2 g (12 mmol) of guanidine hydrochloride. The mixture was stirred briefly and then filtered into a 100-ml round-bottomed flask containing 1.87 g (8.0 mmol) of **14**. The reaction mixture was heated under reflux for 40 h, cooled, concentrated to 10 ml, and diluted with 40 ml of 2-propanol. Cooling at −20 °C for 1 h resulted in the separation of a solid which was collected by filtration, washed with 2-propanol, dried, and recrystallized (charcoal) from 2:1 acetonitrile/methanol to give 1.53 g (70%) of **15** as a yellow, microcrystalline solid, mp 269–270 °C.

Anal. Calcd for $C_{12}H_{16}N_6O_2$: C, 52.16; H, 5.84; N, 30.42. Found: C, 52.26; H, 5.86; N, 30.28.

1-(2,4-Diamino-6-pteridinyl)-3-butanone (16). To a stirred mixture of 1.9 g (7 mmol) of **15** and 25 ml of trifluoroacetic acid at 0 °C was added 0.5 ml of concentrated H_2SO_4. The resulting solution was stirred for an additional 15 min at 0 °C, poured into 50 ml of ice water, stirred for 15 min, and filtered. The collected solid was stirred with 50 ml of 2 N NaOH for 1 h, collected by filtration, and triturated with hot methanol. Cooling and filtration gave 1.31 g (81%) of analytically pure **16** as a light yellow solid, mp 286–287 °C.

Anal. Calcd for $C_{10}H_{12}N_6O$: C, 51.72; H, 5.21; N, 36.19. Found: C, 51.61; H, 5.25; N, 35.95.

1-(2-Amino-3-cyano-5-pyrazinyl)-3-butanol (17). A mixture of 1.52 g (8 mmol) of **13**, 0.16 g (4.2 mmol) of sodium borohydride, and 50 ml of dry methanol was stirred at 0 °C for 10 min and at room temperature for 1 h, and then evaporated to dryness. The residue was dissolved in 20 ml of water and extracted with four 15-ml portions of chloroform. The combined chloroform extracts were dried (Na_2SO_4), filtered, and evaporated to give 0.98 g of a crude solid which was recrystallized from benzene to give 0.83 g (54%) of **17** as a fluffy, yellow solid, mp 101.5–103 °C.

Anal. Calcd for $C_9H_{12}N_4O$: C, 56.24; H, 6.29; N, 29.15. Found: C, 55.64; H, 6.37; N, 28.42.

1-(2,4-Diamino-6-pteridinyl)-3-butanol (18). To a solution of sodium methoxide [from 0.69 g (20 mmol) of sodium in 40 ml of dry methanol] was added 0.57 g (6.0 mmol) of guanidine hydrochloride. After brief stirring, this mixture was filtered into a 100-ml round-bottomed flask containing 0.77 g (4.0 mmol) of **17**. The resulting mixture was heated under reflux for 40 h, cooled, concentrated to 10 ml by evaporation in vacuo, and diluted with 25 ml of 2-propanol. After thorough cooling, the mixture was filtered and the collected solid washed with cold 2-propanol, dried, and recrystallized from 1-propanol to give 0.76 g (81%) of **18** as a microcrystalline, yellow powder, mp 257–258 °C.

Anal. Calcd for $C_{10}H_{14}N_6O$: C, 51.27; H, 6.02; N, 35.89. Found: C, 51.53; H, 5.99; N, 35.89.

2,4-Diamino-6-(2-carboethoxyethyl)pteridine (20). A mixture of 0.44 g (2 mmol) of **19**, 0.26 g (2.2 mmol) of guanidine acetate, and 20 ml of DMF was heated at 120 °C for 39 h. It was then evaporated under reduced pressure and the residual solid triturated with 2-propanol. Filtration gave 0.27 g (52%) of a yellow solid which was recrystallized from 2-propanol, mp 266–267 °C dec.

Anal. Calcd for $C_{11}H_{14}N_6O_2$: C, 50.38; H, 5.38; N, 32.04. Found: C, 50.37; H, 5.44; N, 31.91.

2,4-Diamino-6-phthalimidomethylpteridine (22). A mixture of 2.5 g (9 mmol) of **10**, 1.13 g (9.5 mmol) of guanidine acetate, and 50 ml of DMF was heated at 120 °C for 48 h. The reaction mixture was cooled, diluted with an equal volume of methanol, and filtered. The collected solid was washed copiously with methanol and recrystallized from 1:1 DMF/methanol to give 1.5 g of **22** as yellow needles, mp 338 °C dec.

Anal. Calcd for $C_{15}H_{11}N_7O_2$: C, 56.07; H, 3.45; N, 30.52. Found: C, 55.70; H, 3.56; N, 29.55.

2-(*N,N*-Dimethylformamidylamino)-3-cyano-5-methylpyrazine (23). A mixture of 2.68 g (20 mmol) of **2**, 20 ml of dimethylformamide dimethyl acetal, and 30 ml of dry DMF was stirred at room temperature for 12 h. Evaporation in vacuo then gave a residual oil which solidified on trituration with cyclohexane. Recrystallization from cyclohexane then gave 3.48 g (92%) of **23** as white, fluffy needles, mp 102.5–103.5 °C.

Anal. Calcd for $C_9H_{11}N_5$: C, 57.13; H, 5.86; N, 37.01. Found: C, 57.22; H, 5.68; N, 37.01.

2-(*N,N*-Dimethylformamidylamino)-3-cyano-6-methylpyrazine (24) was prepared in 82% yield from 2-amino-3-cyano-6-methylpyrazine[11] as described above for the conversion of **2** to **23**, yellow needles (from benzene), mp 182.5–183 °C.

Anal. Calcd for $C_9H_{11}N_5$: C, 57.13; H, 5.86; N, 37.01. Found: C, 57.24; H, 5.85; N, 36.92.

2-Amino-3-cyano-6-*n*-propylpyrazine (25). A 5.3-mmol solution of lithium diisopropylamide was prepared in a 100-ml round-bottomed flask fitted with a septum, addition funnel, and gas inlet tube, by syringe addition of 2.2 ml of a 2.4 M solution of *n*-butyllithium to 0.54 g (5.3 mmol) of diisopropylamine in 10 ml of dry THF under nitrogen. This was stirred at −78 °C for 30 min and then to it was added a solution of 0.95 g (5 mmol) of **24** in 40 ml of warm THF. After addition was complete, the reaction mixture was stirred for 1 h at −78 °C and a solution of 0.94 g (6 ml) of ethyl iodide in 10 ml of dry THF was added. Stirring was continued as the reaction mixture was allowed to warm to room temperature. After 20 h the solution was quenched with 25 ml of 10% HCl, heated on a steam bath for 15 min, and then extracted with chloroform. The combined chloroform extracts were dried (Na_2SO_4), filtered, and evaporated to give 0.51 g of a crude solid. Sublimation at 100 °C (0.1 Torr) gave 0.42 g (52%) of **25** as a white, crystalline solid, mp 115–116 °C.

Anal. Calcd for $C_8H_{10}N_4$: C, 59.24; H, 6.21; N, 34.54. Found: C, 59.13; H, 6.21; N, 34.25.

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Registry No.—**1**, 61267-55-8; **2**, 17890-82-3; **3**, 61267-56-9; **4**, 61267-57-0; **6**, 61267-58-1; **7**, 61303-84-2; **8**, 61267-59-2; **9**, 61267-60-5; **10**, 61267-61-6; **11**, 61288-80-0; **13**, 61267-62-7; **14**, 61267-63-8; **15**, 61267-64-9; **16**, 61267-65-0; **17**, 61267-66-1; **18**, 61267-67-2; **19**, 61267-68-3; **20**, 61267-69-4; **21**, 61267-70-7; **22**, 61267-71-8; **23**, 61303-85-3; **24**, 61267-72-9; **25**, 61267-73-0; diethyl malonate Na salt, 996-82-7; sodium cyanide, 143-33-9; ethyl acetoacetate Na salt, 19232-39-4; potassium phthalimide, 1074-82-4; ethyl γ-ethoxyacetoacetate Na salt, 61267-74-1; methyl cyanoacetate Na salt, 24163-38-0; ethylene glycol, 107-21-1; guanidine HCl, 14317-32-9; guanidine acetate, 34771-62-5; dimethylformamide diethyl acetal, 1188-33-6; 2-amino-3-cyano-6-methylpyrazine, 58091-66-0; lithium diisopropylamide, 4111-54-0.

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Highly Stereospecific Dimerization of 5-Formyl-5-methyl-1-pyrazolines. Preparation and Characterization of Stable Carbinolamines (Amino Hemiacetals)

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The unstable 5-methyl-5-formyl-2-pyrazolines **3**, generated in situ by a 1,3-dipolar additon of α-methylpropenal (methacrolein) to α-diazo esters, dimerize in a highly specific way to *meso*-**4**, which are stable carbinolamines. Surprisingly, the latter show no equilibrium with the monomers (pyrazolines) in solution, even at 90 °C in Me_2SO, but they are cleanly transformed into the aminals **5** by a variety of nucleophiles. The conversion of **4** to **5** occurs with retention of configuration at the reacting center, as established by x-ray diffractometry.

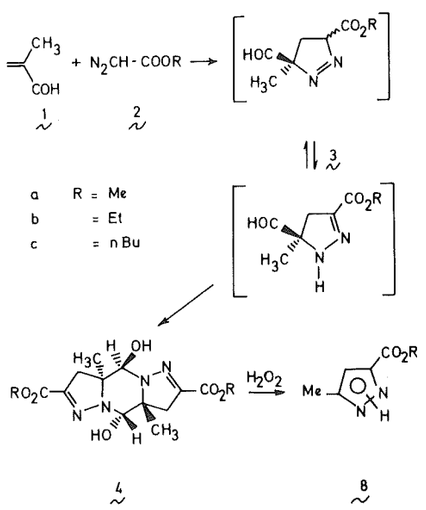
It has been clearly recognized for a long time that the formation of hydrazones, imines, oximes, etc., is a two-step reaction, a carbinolamine being an obligatory intermediate.[1] However, the carbinolamine function itself (also called hemiaminal or amino hemiacetal) has attracted much less attention, although several natural compounds have recently been recognized to possess a stable amino hemiacetal function.[2] From a synthetic point of view, with the exceptions of halogen stabilized molecules,[3] or derivatives of strained cyclopropanones,[4] the dimerization of five-membered heterocycles with a formyl group α to an endocyclic NH constitutes to our best knowledge the only systematic attempts to the synthesis of heterocyclic amino hemiacetals;[5] however, in this case, never was the function clearly and fully characterized, because of nonresolved mixtures and of a dimer–monomer equilibrium in solution. We now report the facile synthesis and characterization of stable carbinolamines from the stereospecific dimerization of substituted 5-formyl-2-pyrazolines.

Results and Discussion

When equimolecular amounts of 2-methylpropenal **1** (methacrolein) and of a diazo ester **2** are mixed in an aprotic solvent at room temperature, a white precipitate begins to appear after about 12 h; its yield, about 45%, is maximum after 2 weeks of standing. Some evolution of nitrogen is also observed; the total amount of gas is proportional to the dilution of the solution, and is quantitative for molar ratios of solvent (CCl_4) to reactants above 50.

The elemental analysis of the precipitates corresponds to equimolecular addition of the starting materials without loss of nitrogen and fits formula **4** (Scheme I) which is further

Scheme I



4 **8**

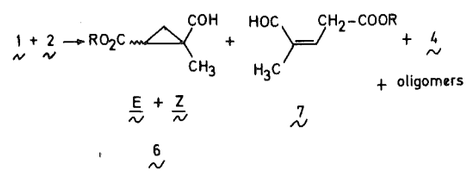
supported by the following spectroscopic characterizations. The main features in the spectra of **4** are, in the infrared, the absence of any peaks due to free hydroxyl group; rather, the sharp and intense absorptions which are seen at about 3500 cm^{-1} indicate hydrogen bonding. Moreover, conjugated azomethine and ester absorptions are seen at respectively 1545 and 1668 cm^{-1}. Although azomethine conjugated esters are quoted to absorb as low as 1680 cm^{-1} in some pyrazolines,[7] such an unusually low frequency is indicative of intermolecular interactions. Indeed, it is shifted up to 1690 cm^{-1} when the –OH function is replaced by $–OCH_3$ (vide infra) or in Me_2SO, while the position of the hydroxyl vibration remains unaffected in the same solvent. On the other hand, the ^1H NMR spectrum shows, beside the AB pattern of the pyrazoline methylene, an uncoupled methyl on a saturated carbon, and an AX system. The latter results from the coupling of the hydroxylic proton with the methine.

Remarkable is the fact that even at 90 °C, no aldehyde (i.e., no equilibrium with **3**) is observed. The AX pattern is still present and indicates a slow exchange in the NMR time scale.

Dipolar additions of diazo compounds to activated double bonds such as **1** are well known and need no further comments, but the stereospecific dimerization of **3** to **4** (Scheme I) which follows the tautomeric equilibrium 1-pyrazoline ⇄ 2-pyrazoline seems to be unique. The mixture complexity made any NMR or IR monitoring of the reaction very difficult. Some points stand out, however. It appeared that the pyrazoline (**3**) concentration is low throughout the reaction (less than an estimated 3–5%, as indicated by integration of the aldehydic region) and, consequently, the dimerization should be fast relative to the pyrazoline formation. The important point in the structure of **4** is the presence of an inversion center, as revealed by the simplicity of both ^1H and ^{13}C NMR spectra. Examination of molecular models did not formally rule out other isomers of **4** on purely steric grounds. However, none of them was observed and that implies a highly stereospecific dimerization of **3**.

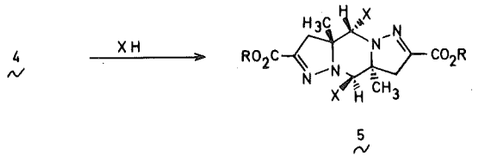
On the other hand, the reaction solution, after filtration of **4** and precipitation by a nonsolvent (hexane), gives a noncrystalline yellow solid, the analysis and spectra of which are indicative of oligomers with a probable polyacetal structure, as described for the reaction of acrolein with ethyl diazoacetate,[7] whereas three additional products are still present in the solution. Their yield increases with dilution and is proportional to the amount of nitrogen evolved. After isolation by VPC, two of them are identified as the *E* and *Z* isomers of cyclopropanes **6**, and the third one is the previously unknown ethyl (*Z*)-4-formyl-3-pentenoate **7** (Scheme II), resulting from

Scheme II



a formal insertion of a carbomethoxycarbene into the CH group of methacrolein. Oxidation of **4** by activated manganese dioxide or hydrogen peroxide allowed the isolation of pyrazoles **8** in moderate yields[8] (Scheme I). Substituting the hydroxyl group of the carbinolamine function appears to have broad synthetic potentialities, that are illustrated in Scheme III by some chosen derivatives resulting from the reaction of

Scheme III



4 with quite various nucleophiles (e.g., alcohols, phenol, aniline, and pyrazole). A complete retention of configuration obtains in these reactions: crystals of **5a** (R = Me) and of **4b** have been analyzed by x-ray diffractometry and the structure fully confirmed.[9] The central piperazine ring is in a chair conformation with a methoxy group trans to the vicinal methyl, and the ester carbonyl (1695 cm^{-1}) lies in the plane of the conjugated azomethine double bond.

On the other hand, crystals of **4b** have the same overall stereochemistry as **5**, the hydroxyl is also trans to the α-methyl,[10] and the conversion of **4** into **5** occurs with retention of configuration. The above observation ought to reflect some kind of intramolecular participation since purely steric effects should not be large enough to promote a total retention at the reacting center.

Experimental Section

Boiling points and melting points are uncorrected. ^1H NMR spectra were recorded on Varian T60 or HA-100 spectrometers; ^{13}C spectra

on a Brucker HFX 90 instrument at 22.63 MHz. All chemical shifts are measured in parts per million (δ) downfield from Me_4Si or HMDS. The ^{13}C resonance frequencies have been assigned by comparison with a nondecoupled spectrum of **5a** (Alk = CH_3) in $CDCl_3$.

Infrared spectra were obtained on a Perkin-Elmer Model 21 spectrometer and frequencies are given in cm^{-1}.

Preparative VPC was carried out on a Varian 2800 instrument; the columns used were 16 × 0.75 in., 20% SE-30 on Chromosorb W 30–60.

The following descriptions are typical for the preparation of **4** and **5**.

I. Preparation of 2,7-Diethoxycarbonyl-3a,8a-dimethyl-4,9-dihydroxy-3*H*,8*H*-dipyrazolino[1,5-*a*:5′,1′-*d*]-4*H*,9*H*-pyrazine (4b). In 5 mL of benzene are added 1.14 g (1 mmol) of ethyl diazoacetate and 0.77 g (1.1 mmol) of 2-methylpropenal. The solution is let without stirring at room temperature for several days and **4** slowly precipitates. After 10 days, the yield is about 40% but some precipitation still occurs during the following weeks. The solid is filtered, washed with benzene, and crystallized in acetone.

4b (R = C_2H_5): mp 219–224 °C dec; IR (OH, COOEt, C=N, respectively) (KBr) 3497, 1668, 1547 cm^{-1}; (Nujol) 3500, 1665, 1547 cm^{-1}; (Me_2SO) 3500, 1690, 1537 cm^{-1}; other absorptions (KBr) 1340 (s), 1292 (m), 1266 (s), 1250 (m), 761 (s), 752 (s), 732 cm^{-1} (m); NMR (Me_2SO-d_6, HMDS, 100 MHz) δ 6.47 (d, 1, *J* = 3.75 Hz, OH), 5.08 (d, 1, *J* = 3.75 Hz, CH), 4.10 (q, 2, CH_2CH_3), 3.28 and 2.50 [m, 2, *J* = 16.75 Hz, CH_2 (AB)], 1.24 (s, 3, CH_3), 1.16 (t, 3, CH_2CH_3); ^{13}C NMR (Me_2SO-d_6, Me_4Si–C_6D_6 with proton noise decoupling) 159.6 (COO), 132.0 (C=N), 82.6 (COH), 65.6 (CCH_3), 39.8 [CH_2 (AB)], 24.9 (CCH_3); ethyl ester 59.0 (CH_2), 13.9 ppm (CH_3). Anal. Calcd for $C_{16}H_{24}N_4O_6$: C, 52.17; H, 6.52; N, 15.22. Found: C, 52.2; H, 6.6; N, 15.2.

4a (R = CH_3), mp 208.5–210 °C dec. Anal. Calcd for $C_{14}H_{20}N_4O_6$: C, 49.41; H, 5.88; N, 16.47. Found: C, 49.5; H, 6.0; N, 16.5.

4c (R = *n*-Bu), mp 181–183 °C dec. Anal. Calcd for $C_{20}H_{32}N_4O_6$: C, 56.60; H, 7.55; N, 13.20. Found: C, 56.7; H, 7.7; N, 13.4.

A. Preparation of Aminoacetal 5a from 4a. 4a is refluxed in methanol with stirring. After dissolution heating is continued for about 0.5 h. Upon slow cooling, **5a** precipitates: mp 218–224 °C; IR (KBr) 3018 (w), 2850 (w), 1695 (s, $COOCH_3$), 1545 (s, C=N), 1333 (s), 763 (s), 756 (s), 727 cm^{-1} (m); NMR ($CDCl_3$, Me_4Si, 100 MHz) δ 4.91 (s, 1, CH), 3.84 (s, 3, CO_2CH_3), 3.34 (s, 3, $–OCH_3$), 3.62–2.69 [m, 2, *J* = 17.2 Hz, CH_2 (AB)], 1.41 (s, 3, CH_3). Anal. Calcd for $C_{16}H_{24}N_4O_6$: C, 52.17; H, 6.52; N, 15.22. Found: C, 52.3; H, 6.6; N, 15.3.

B. Preparation of 5b (R = Et). 4b (2 g) in 15 mL of 2,2,2-trifluoroethanol is heated at 60 °C for 3 h. After cooling, **5b** is precipitated by addition of ether and crystallized from carbon tetrachloride: yield 86%; mp 233–236 °C; IR (KBr) 1720 (s, ester), 1552 (s, C=N), 757 (s), 747, 668 cm^{-1} (m); NMR ($CDCl_3$, HMDS, 60 MHz, only quoted are the absorptions of the substituted part of the molecule) 3.7 (q, 2, *J* = 8 Hz, $–CH_2CF_3$), 5.03 (s, 1 H, CH methine). Anal. Calcd for $C_{20}H_{26}N_4O_6F_6$: C, 45.11; H, 4.89; N, 10.53. Found: C, 45.0; H, 4.9; N, 10.5.

C. Preparation of 5c (R = Et). 4b (0.5 g) and 3 g of phenol are heated at 40 °C overnight. The excess of phenol is sublimed under vacuum and the residue crystallized from toluene: yield 61%; mp 231 °C; IR (KBr) no OH, 1693 (s, ester), 1556 (s, C=N), 756 (s), 734 cm^{-1} (m); NMR ($CDCl_3$, HMDS, 60 MHz) δ 7.10 (m, 5, C_6H_5), 5.73 (s, 1, CH). Anal. Calcd for $C_{28}H_{32}N_4O_6$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.5; H, 6.6; N, 10.6.

D. Preparation of 5d. 4b (2 g) is heated in 5 mL of *p*-fluoroaniline for 3 h at 100 °C, 30 mL of benzene is then added, and the solution is refluxed for 1 h. After evaporation of the solvent, the residue is crystallized from acetonitrile: yield 79%; mp 242 °C; IR (KBr) 3450 (s, NH), 1680 (s, ester), 1540 (m), 1510 (s), 823 cm^{-1} (s). Anal. Calcd for $C_{28}H_{32}N_6O_4F_2$: C, 60.65; H, 5.78; N, 15.16. Found: C, 61.0; H, 5.8; N, 15.2.

E. Preparation of 5e. 4b (1.5 g) and 2 g of pyrazole are refluxed overnight in 830 mL of acetone. After filtration, the solvent is evaporated under vacuum, the solid kept under vacuum for a few hours, and the residue crystallized from a mixture of benzene–cyclohexane: yield 42%; mp 228–232 °C; IR (KBr) no OH, 1714 (s, ester), 1545 (s, C=N), 1212 (s), 772 (m), 763 (s), 753 cm^{-1} (s); NMR ($CDCl_3$, HMDS, 60 MHz) δ 7.60 (d, 1, *J* = 2 Hz, pyrazole), 7.45 (large d, 1, H pyrazole), 6.20 (t, 1, H_4 pyrazole), 6.08 (s, CH).

II. Preparation of 3(5)-Carboethoxy-5(3)-methylpyrazole (8). The product **4b** (R = Et) is dissolved with stirring in an excess of hot H_2O_2 (15%) for 5 min. After cooling, the solution is extracted several times with chloroform, the organic solution dried ($CaSO_4$), and the solvent evaporated under vacuum. The oily residue is crystallized twice from hexane (38%): mp 82–83 °C, identical with the literature data;[11] (KBr) 3300–2900 (s, NH), 1725 cm^{-1} (s, COOEt); NMR ($CDCl_3$, HMDS, 60 MHz) δ 11.73 (s, 1, NH), 6.47 (s, 1, H aromatic), 4.25 (q, 2, CH_2CH_3), 2.26 (s, 3, CH_3), 1.22 (t, 3, CH_2CH_3).

III. Reactions in Diluted Medium. Preparation of 6 and 7. To a solution of 1.7 mL (20 mmol) of α-methylacrolein in 25 mL of benzene is added 2.1 mL (20 mmol) of ethyl diazoacetate. The mixture is stirred at 40 °C until the evolution of nitrogen is over (80% in volume). The solid **4** is filtered off, the solvent eliminated, and the crude mixture distilled under vacuum before preparative VPC. The crude yield of **6** and **7** is about 80%.

IV. (*Z*)-1-Formyl-1-methyl-2-carboethoxycyclopropane (6, R = Et): bp 43–46 °C (1 mm); IR (neat) 3060 (w, cycle), 1735 (s, COOEt), 1720 (s, CHO), 1029, 878 cm^{-1}; NMR ($CDCl_3$, Me_4Si, 60 MHz) δ 9.09 (s, 1, CHO), 4.05 (q, 2, OCH_2CH_3), 2.2–1.5 (m, 3, ring), 1.17 (t, 3, OCH_2CH_3), 1.15 (s, 3, CH_3).

V. (*E*)-1-Formyl-1-methyl-2-carboethoxycyclopropane (6, R = Et): NMR ($CDCl_3$, Me_4Si, 60 MHz) δ 8.66 (s, 1, CHO), 2.3–1.8 and 1.6–1.1 (m, 3, ring), 1.25 (s, 3, CH_3).

Anal. (mixture of both isomers of **6**) Calcd for $C_8H_{12}O_3$: C, 61.55; H, 7.69. Found: C, 61.6; H, 7.8.

VI. Ethyl (*Z*)-4-Formyl-3-pentenoate (7): 10%; bp 52–54 °C (1 mm); IR (neat) 1749 (s, COOEt), 1700 (s, CHO), 1030 (s), 812 cm^{-1} (w); NMR ($CDCl_3$, Me_4Si, 60 MHz) δ 9.24 (s, 1, CHO), 6.53 (d of t, 1, ^3J = 7.0, ^4J = 1.4 Hz, H vinyl), 4.11 (q, 2, OCH_2CH_3), 3.23 (d of d, 2, ^3J = 7.0, ^5J = 1.0 Hz, CH_2), 1.66 (m, 3, CH_3).

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Registry No.—**1**, 78-85-3; **2a**, 6832-16-2; **2b**, 623-73-4; **2c**, 24761-88-4; **4a**, 61597-89-5; **4b**, 60323-59-3; **4c**, 61597-90-8; **5a** (R = Me), 55199-74-1; **5b** (R = Et), 61597-91-9; **5c** (R = Et), 61597-92-0; **5d** (R = Et), 61597-93-1; **5e** (R = Et), 61597-94-2; *E*-**6** (R = Et), 13949-97-8; *Z*-**6** (R = Et), 13950-14-6; *Z*-**7** (R = Et), 61597-95-3; **8**, 4027-57-0; methanol, 67-56-1; 2,2,2-trifluoroethanol, 75-89-8; phenol, 108-95-2; *p*-fluoroaniline, 371-40-4; pyrazole, 288-13-1.

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