0.44 g, 98%). Recrystallization gave **18** as yellow crystals, mp 234–6 °C dec. IR: 3360, 3110, 1670, 1620, 1600, 1510, 1480, 1235, 1120, 1015 cm^{-1}. ^1H NMR: δ 6.91 (H_6), 7.61 (H_7) ($J_{6,7}$ = 9.46 Hz). ^{13}C NMR (d_6-DMSO): δ 106.23 (C_8), 121.58 (C_6), 121.84 (C_7), 160.03 (C_9), 161.97 (C_5). MS, *m/z*: 152 (parent ion), 79 (base peak), 52. HRMS: $C_5H_4N_4O_2$ requires 152.0334, found 152.0328.

5-Acetamidofurazano[4,5-*b*]pyridine 1-Oxide (19). 5-Aminofurazano[4,5-*b*]pyridine 1-oxide (**18**) (0.10 g, 0.7 mmol) was added to glacial acetic acid (3 mL) and acetic anhydride (3 mL) and heated under reflux overnight. The solution was cooled and quenched in water (30 mL) and neutralized with potassium carbonate. Extraction with dichloromethane (3 × 25 mL) gave a pale yellow solid (0.125 g, 98%). Recrystallization from ethanol gave **19** as a pale yellow powder, mp 187–90 °C. IR: 3250, 1710, 1600, 1580, 1500, 1430, 1400, 1325, 1255, 1200, 1110, 1030, 1005, 995, 835 cm^{-1}. ^1H NMR: δ 2.31 (s, 3 H, $COCH_3$), 7.99 (H_6), 8.34 (H_7) ($J_{6,7}$ = 9.70 Hz). ^{13}C NMR (d_6-DMSO): δ 24.44 (CH_3), 107.15 (C_8), 120.57 (C_6), 124.43 (C_7), 158.01 (C_9), 170.78 (CO and C_5). MS, *m/z*: 194 (parent ion), 152, 95, 79, 64, 52, 43 (base peak). HRMS: $C_7H_6N_4O_3$ requires 194.0440, found 194.0432.

Single-Crystal X-ray Structure of Tetrazolo[1,5-*f*]furazano[4,5-*b*]pyridine 1-Oxide (13). Tetrazolo[1,5-*f*]-furazano[4,5-*b*]pyridine 1-oxide (**13**) crystallized as salmon-colored platelets from benzene in space group $P2_12_12_1$, Z = 4, D_x = 1.719. A crystal of dimensions 0.06 × 0.32 × 0.56 mm with (001) platelet faces was used for data collection on a Nicolet R3 instrument. Unit cell parameters a = 5.961 (1), b = 9.968 (2), and c = 11.589 (2) Å were determined from a least-squares fit of 25 computer-centered reflections with 2θ values ranging from 8 to 28° (Mo K_α). $2\theta/\theta$ intensity data were collected at room temperature (291 K) at variable scan speeds of 2–6°/min over a 2θ range 4–54° for octants $\bar{h}k\bar{l}$, $\bar{h}kl$, $hk\bar{l}$, hkl with monochromated Mo K_α radiation. Three check reflections (210), (01$\bar{2}$), and ($\bar{1}$41), collected every 93 reflections, were constant. All data reduction and structure solution/refinement calculations were performed with SHELXTL.[23] The 3311 observations were corrected for Lorentz and polarization effects. Because of the crystal shape, numerical Gaussian absorption corrections (μ = 1.31 cm^{-1}) were applied; minimum and maximum transmission factors were 0.957 and 0.991, respectively. Equivalent reflections were merged (R_{merge} = 0.0106) to yield 1511 unique data of which 1370 with $|F_o| > 4\sigma(F)$ were used in refinement. With the inclusion of four additional reflections in the starting set, the positions of all C, N, O atoms were observed on the first E_{map} obtained by direct, multisolution methods. All N, O atoms and C(1), C(5) were refined anisotropically; C(2), C(3), C(4) were refined isotropically. The two H atoms were refined as "riding" on their adjacent carbon atoms but with unconstrained isotropic thermal parameters. The 105 parameters were refined with the blocked cascade algorithm of SHELXTL[23] and with weights $w = 1/[\sigma^2(F) + 0.0009F^2]$. Maximum shift/esd ratios were less than 0.05 for the final refinement cycles. Final agreement factors were R = 0.040, R_w = 0.054, goodness of fit = 1.39, where $R = \sum(|F_o| - |F_c|)/\sum|F_o|$ and $R_w = [\sum w(|F_o| - F_c|)^2/\sum(|F_o|)^2]^{1/2}$. Final difference Fourier maps had peaks and troughs ranging from +0.40 to 0.28 $e^-/Å^3$. Crystallographic data, including final atomic coordinates, have been deposited.

(23) SHELXTL, version 4.1, Nicolet XRD (1984).

Acknowledgment. Fourier transform infrared spectra were recorded by M. P. Nadler and low resolution mass spectra were recorded by D. A. Fine, both of the Naval Weapons Center. High resolution mass spectra were recorded by R. Minard and J. Blank at the Mass Spectrometry Facility, Department of Chemistry, Pennsylvania State University; A. J. Freyer of the Department of Chemistry, Pennsylvania State University, is also thanked for assistance with certain NMR experiments.

Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond lengths and angles, and anisotropic thermal parameters for **13** (3 pages); observed and calculated structure factors for **13** (9 pages). Ordering information is given on any current masthead page.

Reaction of 4,4-Diethyl-3,5-pyrazolidinedione with Carboxylic Acid Anhydrides. N-Acylation vs O-Acylation

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The acylation of 4,4-diethyl-3,5-pyrazolidinedione with carboxylic acid anhydrides was investigated in order to establish the position(s) of acylation on the pyrazolidine ring. The reaction was carried out with acetic, propanoic, butanoic, pentanoic, chloroacetic, and benzoic anhydrides. Both a monoacylated and a diacylated product were isolated in each case. IR, UV, ^1H and ^{13}C NMR, and mass spectroscopic data were not diagnostic of the structures. X-ray crystallography showed that the products were N-acylated and N,N-diacylated compounds, respectively. No N,O-diacylated products were obtained. ^{15}N NMR spectroscopy appears to be a useful spectroscopic technique for establishing the position(s) of acylation.

Several reports of acylation reactions between 3,5-pyrazolidinediones and carboxylic acid anhydrides or acid chlorides yielding monoacylated and/or diacylated products have been published.[1-8] The published results are conflicting in that the products have been reported to be both N-acylated derivatives **2** and **3**[1-6] and O-acylated derivatives **2A** and **3A**.[7,8] No example of an N,O-diacylated derivative **4** has been reported. The assignments of the

(1) Godin, J.; Le Berre, A. *Bull. Soc. Chim. Fr.* **1968**, *10*, 4210.
(2) Dormoy, M.; Godwin, J.; Le Berre, A. *Bull. Soc. Chim. Fr.* **1968**, *10*, 4222.
(3) Zinner, G.; Moll, R.; Boelke, B. *Arch. Pharm.* **1966**, *299*, 441.
(4) Nasr, H.; El-Zanfally, S.; Khalifa, M.; Abu-Shady, H. *Pharmazie* **1976**, *31*, 7745.
(5) Nasr, H.; El-Zanfally, S.; Khalifa, M. *Egypt. J. Pharm. Sci.* **1976**, *15*, 345.
(6) Kornet, M. J.; Thorstenson, J. H.; Lubawy, W. C. *J. Pharm. Sci.* **1974**, *63*, 1090.
(7) Ruhkopf, H. *Chem. Ber.* **1940**, *73B*, 820.
(8) Gillis, B. T.; Izydore, R. A. *J. Org. Chem.* **1969**, *34*, 3181.

0022-3263/90/1955-3761$02.50/0

Scheme I

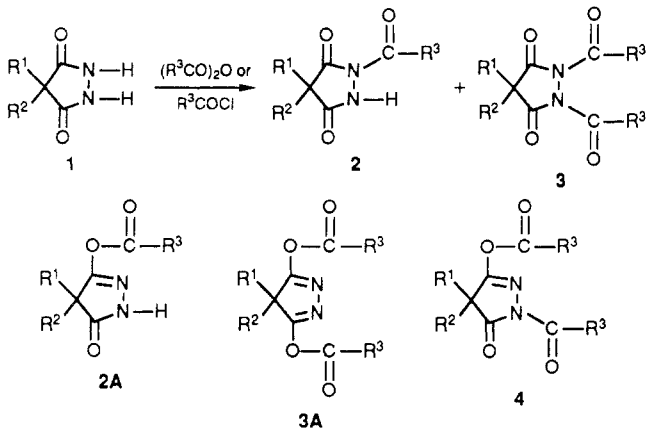


Table I. Products Isolated from the Reaction of 4,4-Diethyl-3,5-pyrazolidinedione (1a) with Carboxylic Acid Anhydrides

anhydride	monoacylated product yield, %	diacylated product yield, %
acetic	94,[a] 11[b]	0,[a] 76[b]
propanoic	53,[c] 12[d]	0,[c] 34[d]
butanoic	65,[e] 1[d]	0,[e] 28[d]
pentanoic	34,[f] 0[d]	0,[f] 21[d]
chloroacetic	70,[g] 0[h]	2,[g] 85[h]
benzoic	74,[c] 0[c]	2,[c] 82[i]

[a] 1.75:1 anhydride/1a was heated at reflux in chloroform for 1 day. [b] 4:1 anhydride/1a was heated at reflux in chloroform for 3 days. [c] 1:1 anhydride/1a was heated at reflux in chloroform for 5 days. [d] 6:1 anhydride/1a was heated at reflux in chloroform for 5 days. [e] 1:1 anhydride/1a was heated at reflux in chloroform for 3 days. [f] 1:1 anhydride/1a was heated at reflux in 1,2-dimethoxyethane for 14 days. [g] 1.3:1 anhydride/1a was heated at reflux in chloroform for 3 days. [h] 6.7:1 anhydride/1a was heated at reflux in chloroform for 3 days. [i] 6.5:1 anhydride/1a was heated at reflux in chloroform for 7 days.

structures of the various products were made on the basis of the available IR, UV, and ^{1}H NMR spectral data[1,2,4-6,8] or without explanation.[3,7]

In the current study we investigated the reaction between 4,4-diethyl-3,5-pyrazolidinedione with carboxylic acid anhydrides in order to establish the position(s) of acylation on the pyrazolidine ring. It was also of interest to find a routine spectroscopic method for making this assignment.

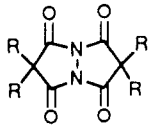
Results and Discussion

The acylation of 4,4-diethyl-3,5-pyrazolidinedione (**1a**, $R^1 = R^2 = Et$) with a series of carboxylic acid anhydrides was carried out in chloroform or 1,2-dimethoxyethane solution. Both monoacylated and diacylated products were isolated from the reaction of each of the anhydrides. The products and their percent yields are presented in Table I.

It was necessary to adjust the reaction conditions for each anhydride used in order to optimize the yields of the products. Thus, in the reaction of the aliphatic anhydrides, both the reaction time and reaction temperature were increased as the number of carbon atoms in the carbon chain increased. In general, the monoacylated compounds were the major products when the reactions were carried out with stoichiometric or near-stoichiometric quantities of the anhydrides, and diacylated compounds were the major products when the reactions were carried out in the presence of excess quantities of the anhydrides. The wide variety of acylated products obtained shows that the synthetic method employed has a broad general applicability for the preparation of mono- and diacylated 3,5-pyrazolidinediones.

The diacylated products are sensitive to moisture. Heating these products in EtOH/H_2O (50:50) for 10–15 min caused their hydrolysis to the monoacylated analogues. The diacylated products were also partially decomposed on storage in capped vials for several months. The odors of their carboxylic acid decomposition products were readily discernible on opening the vials.

The IR spectra of the monoacylated products showed NH absorptions at 3215–3250 cm^{-1} as well as two carbonyl absorptions. A medium-intensity peak appeared at 1740–1750 cm^{-1}, and a strong-intensity peak appeared at 1700–1715 cm^{-1}. The diacylated products showed their carbonyl absorptions as a single strong-intensity peak between 1740 and 1750 cm^{-1}. The IR results are not definitive. The higher frequency carbonyl absorptions can be interpreted as corresponding to ester types, but they are also similar to those found in the pyrazolo[1,2-*a*]-pyrazole-1,3,5,7-tetraones (**5**), which give two absorptions



between 1735 and 1792 cm^{-1}.[8,9] In the latter compounds the carbonyl group absorptions are expected to appear at higher frequencies than those of the monoacylated and diacylated products, owing to the effect of the five-membered rings.

The UV (EtOH) spectra of the monoacylated products showed two absorptions, which appeared at 219–221 nm (ϵ 7800–9000) and 251–257 nm (ϵ 3450–4150), respectively. The diacylated derivatives gave only one absorption at 214–217 nm (ϵ 8000–9000). The absorption wavelengths of the diacylated derivatives are intermediate between those exhibited by pyrazole (UV (EtOH) λ_{max} 210 nm (ϵ 6500)) and **5** (R = Et) (UV (EtOH) λ_{max} 233 nm (ϵ 11 200)).[8] The addition of (acyloxy)auxochromes to positions 3 and 5 of pyrazole might be expected to increase its absorption to a longer wavelength. Therefore, the UV results are not definitive.

The ^{1}H NMR spectra of the acylated products were recorded at 400 MHz. The hydrogens on the α-carbons of the acyl group substituents were found at δ 2.50–2.98. This chemical shift range does not favor either the N- or the O-acylated structures. The diacylated products gave only one peak for the α-hydrogens in this region at nearly the same chemical shifts as those observed for the corresponding monoacylated analogues, indicating that (1) the position of acylation, N vs O, was the same in the mono and diacylated derivatives, (2) the N,O-diacylated structures (**4**) were not produced, and (3) the two acyl groups are in equivalent positions on the ring. The two ethyl groups at position 4 of the ring were found to be equivalent in both the monoacylated and diacylated products. This is consistent both with the O-acylated structures and with the N-acylated structures, provided that the acyl group is planar or nearly planar to the pyrazolidine ring in the mono-N-acylated structures and that the acyl groups are planar or nearly planar to the pyrazolidine ring or situated anti to each other on it in the N,N-diacylated structures.

(9) Moldaver, B. L.; Papirnik, M. P. *Khim. Geterotsikl. Soedin* **1971**, *7*, 1097.

The ^{13}C NMR spectra of the acylated products were recorded in chloroform-*d* at 100 MHz. The two ethyl groups at position 4 of the ring were found to be equivalent in all of the derivatives and were observed near δ 8.9 and 28.9 in each case. The nonprotonated carbon at position 4 appeared near δ 57.0. The monoacylated compounds gave peaks at δ 169.8 and 171.3 for the ring carbonyl carbons at positions 3 and 5, respectively. The carbonyl carbons of the acyl substituents were observed at δ 163–167. The diacylated compounds gave a single peak for the ring carbonyl carbons at positions 3 and 5 near δ 171 and a peak for the carbonyl carbons of the acyl substituents at δ 161–169. In general, the data led to the same conclusions as those made from the ^1H NMR data. The peaks observed from δ 161–172 were not informative for assigning the sites of acylation because amide, imine, and ester carbonyl carbons all absorb in this region.[10]

In a previous report the chemical shift positions of the acetyl protons of the mono- and diacetylated derivatives of **1**, which were observed at δ 2.53 and 2.55, respectively, were used to assign the structures as the N-substituted compounds **2** (R = Me) and **3** (R = Me) because these chemical shifts were analogous to those observed for the N-mono- and N,N-diacetylated succinic hydrazides, which appeared at δ 2.50 and 2.44, respectively.[1] The assignment of the structures of the latter derivatives as N-substituted rested on the observation that the alkaline hydrolysis of the diacetylated succinic hydrazide derivative produced diacetylhydrazine. It was also reported that phthalic hydrazide gave the N-acetylated derivative when heated with acetyl chloride in pyridine and the O-acetylated derivative when its potassium salt was treated with acetyl chloride at room temperature.[1] The structures of the derivatives were assigned from the ^1H NMR chemical shift positions of their acetyl protons, which appeared at δ 2.67 for the N-acetylated structure and δ 2.47 for the O-acetylated structure. The derivative that showed its acetyl protons at δ 2.67 was assigned as the N-acetylated structure because this chemical shift was near to that observed for the acetyl protons of *N*-acetylphthalazone, which appeared at δ 2.78.[1] If these assignments are correct, then acetyl protons having a chemical shift near δ 2.5 are N-acetylated when substituted on succinic hydrazide and O-acetylated when substituted on phthalic hydrazide, and the chemical shift positions of the acetyl protons are not analogous in these two ring systems. On the basis of these observations, the assignment of the structures of the acetylated 3,5-pyrazolidinediones as the N-substituted compounds is tenuous. The ^1H NMR chemical shifts of the acetyl protons of the acetylated 3,5-pyrazolidinediones do not necessarily correspond to those of the succinic hydrazide derivatives.

The electron-impact mass spectra of the acylated products were recorded at 70 eV. With the exception of the diacetylated and the mono- and bis(chloroacetylated) products, all of the products gave a base peak at the mass corresponding to that of their acyl substituents. These peaks resulted from fragmentation of the respective molecular ions by α-cleavage. All of the products showed an odd-electron ion peak at m/z 156. The appearance of this peak is consistent with the loss of one or two ketene molecules from the molecular ions of the monoacylated and diacylated products, respectively. In the monoacylated series the relative intensity of the peak at m/z 156 was 100% and 88% for the chloroacetyl- and acetyl-substituted products, respectively, and 5–30% for the C_3–C_5 monoacylated products. In the diacylated series the peak intensity at m/z 156 decreased from 100% to 8% as the size of the acyl substituents increased from two to five carbons. The losses of the ketene fragments can be accounted for by fragmentation mechanisms involving hydrogen atom rearrangements from the α-carbon of the acyl groups to either a ring nitrogen atom or a ring carbonyl oxygen followed by α-cleavage.[11] This type of mechanism can account for the peak at m/z 156 for the N-acylated, O-acylated, N,N-diacylated, and O,O-diacylated structures. There are no grounds for favoring the N-acylated or O-acylated structures on the basis of mass spectral data.

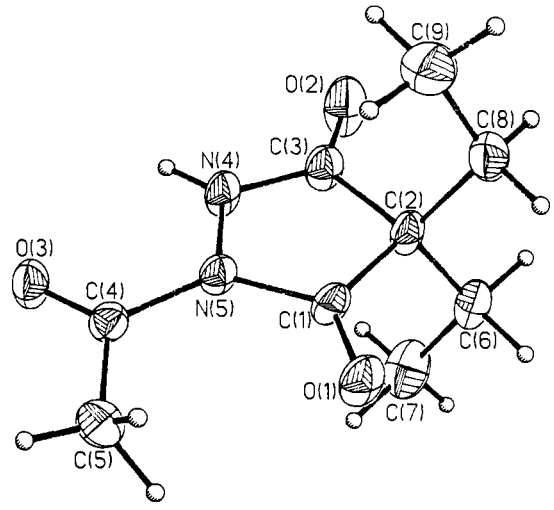


Figure 1. X-ray crystal structure of 1-acetyl-4,4-diethyl-3,5-pyrazolidinedione (**6**, R = Me).

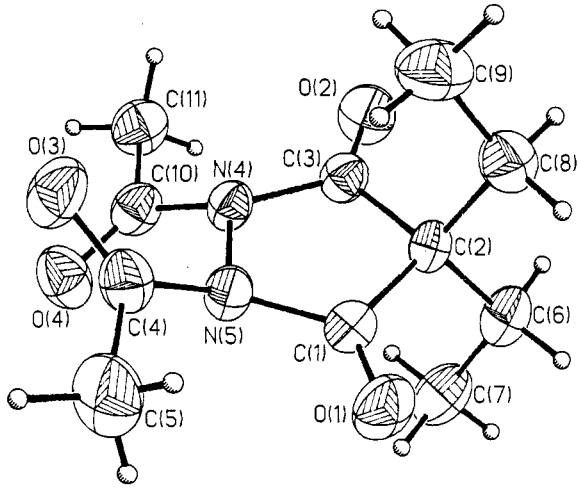
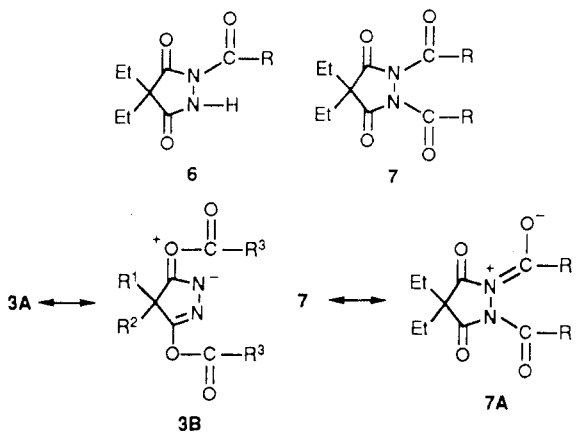


Figure 2. X-ray crystal structure of 1,2-diacetyl-4,4-diethyl-3,5-pyrazolidinedione (**7**, R = Me).

The monoacetylated and diacetylated products were analyzed by X-ray crystallography. The crystals of the diacetylated compound rapidly degraded in the open atmosphere, and it was necessary to seal the crystals in a Lindmann glass capillary in order to collect the data. The results showed that both products are N-acetylated. The monoacetylated product is 1-acetyl-4,4-diethyl-3,5-pyrazolidinedione (**6**, R = Me), and the diacetylated derivative is 1,2-diacetyl-4,4-diethyl-3,5-pyrazolidinedione (**7**, R = Me). The X-ray structures are shown in Figures 1 and 2. The pyrazolidine rings in both compounds are planar

(10) Levy, G. C.; Lichter, R. L.; Nelson, G. L. *Carbon-13 Nuclear Magnetic Resonance Spectroscopy*, 2nd ed.; John Wiley and Sons: New York, 1980; chapters 4 and 5.

(11) McLafferty, F. W. *Interpretation of Mass Spectra*, 3rd ed.; University Science Books: Mill Valley, CA, 1980; chapter 4.



within 0.003 Å. In the N-monoacetylated compound **6** (R = M) the acetyl carbonyl group is nearly coplanar with the five-membered ring. The dihedral angle between the planes of the acetyl group and the pyrazolidine ring is 7.2°, and the ethyl groups at position 4 lie equidistant above and below the ring, respectively. In the N,N-diacetylated compound **7** (R = Me), the two acetyl groups are anti to each other and are quite far removed from coplanarity. The acetyl carbon atoms lie 0.83 and 0.46 Å above and below the plane of the ring, respectively, and the dihedral angles of the planes of the acetyl groups to the plane of the ring are 37.5° and 23.3°, respectively. The two ethyl groups do not lie exactly equidistant above and below the plane of the ring. The ethyl group that is syn to the acetyl group having the larger dihedral angle to the ring lies farther removed from the plane of the ring than does the ethyl group that is anti to it. On the basis of the X-ray data and the spectroscopic data discussed above, it can be concluded that all of the monoacylated products are N-acylated compounds **6** and all of the diacylated products are N,N-diacylated compounds **7**.

The X-ray data offer an explanation as to why compounds **6** are relatively stable to water and compounds **7** are not, assuming that all derivatives of each compound show similar structural features. The acyl group substituents in compounds **6** are nearly coplanar to the ring and are conjugated to the lone pair of electrons on the ring nitrogen. Thus, these resonance-stabilized groups are resistant to hydrolysis. The acyl group substituents in compounds **7** are twisted out of conjugated with the lone pairs of electrons on the ring nitrogens. They are not stabilized by resonance and, as a result, are more susceptible to attack by water.

A study of the 40.54-MHz ^{15}N NMR spectra of compounds **7** was made. The data are presented in Table II.[12] The chemical shifts ranged from δ 179 to 186 relative to external ammonia. This range is in the region characteristic of nitrogen atoms that are pyrrole-like. The chemical shift of the nitrogen atom in 3,5-pyrrolidinedione (**8**) in acetone, for example, is δ 176.9.[13] Nitrogen atoms that are pyridine-like are usually observed much farther downfield in the region of δ 240–400.[13] The nitrogen chemical shifts in 1-methylpyrazole (**9**) in chloroform are illustrative. The pyrrole-like nitrogen is observed at δ 199.4, and the pyridine-like nitrogen is observed at δ 305.5.[14] The ^{15}N NMR data for the diacylated compounds

Table II. ^{15}N NMR Spectral Data of the N,N-Diacylated 4,4-Diethyl-3,5-pyrazolidinediones 7

R	chem shift,[a,b]	R	chem shift,[a,b]
Me	183.7	*n*-Bu	183.2
Et	185.1	CH_2Cl	179.2
n-Pr	185.7	Ph	180.1

[a] $CDCl_3$ was the solvent. [b] The chemical shifts are relative to external liquid ammonia.

are consistent with compounds **7**. The nitrogen chemical shifts in compounds **3A** might be expected to appear somewhat upfield from that of the pyridine-like nitrogen in **9**, depending on the extent to which resonance form **3B** contributes to the resonance hybrid. However, it is unlikely that these nitrogens would be shielded via resonance sufficiently enough to cause their chemical shifts to appear in the pyrrole-like region. In contrast, the X-ray results indicate that resonance forms **7A** do not significantly stabilize compounds **7**. Therefore, the nitrogen chemical shifts of compounds **7** can be expected to be near that of **8**.

Attempts were made to prepare the *O*-benzoyl derivative **2A** ($R^1 = R^2 = Et$, $R^3 = Ph$) by reacting the sodium salt **10** of **1a** with benzoyl chloride (**11**).[1] The reactions were carried out by heating equimolar quantities of **10** and **11** under reflux in dry 1,2-dimethoxyethane under nitrogen for up to 4 days followed by filtration of the reaction solids and evaporation of the solvent. The residues contained the *N*-benzoyl product **6** (R = Ph) (54% after 4 days) as shown by IR and melting point behavior. There was no evidence for the formation of the *O*-benzoyl compound **2A** ($R^1 = R^2 = Et$, $R^3 = Ph$).

The X-ray and ^{15}N NMR chemical shift data show that the acylated products from **1a** and carboxylic acid anhydrides are substituted on nitrogen and that those investigators who had previously reported N-acylated structures were correct.[1-6] However, in the absence of authentic samples of both N- and O-acylated 3,5-pyrazolidinediones, the IR, UV, ^1H and ^{13}C NMR, and mass spectroscopic data do not convincingly argue for one site of substitution over the other. However, ^{15}N NMR spectroscopy appears to be a useful spectroscopic technique for establishing the position(s) of acylation. If examples of O-acylated and O,O-diacylated compounds were available, then further correlations of spectral characteristics vs site(s) of acylation might become apparent.

Experimental Section

Melting points and boiling points are uncorrected. IR spectra were recorded on a Beckman Acculab 10 spectrophotometer. UV spectra were taken on a Beckman DU-7 UV–vis spectrophotometer. ^1H NMR (400 MHz), ^{13}C NMR (100 MHz), and ^{15}N NMR (40.54 MHz) spectra were recorded on a Varian XL-400 spectrometer at the University of North Carolina at Chapel Hill. ^1H and ^{13}C NMR chemical shifts are reported relative to internal tetramethylsilane. ^{15}N NMR chemical shifts are reported relative to external ammonia. Mass spectra were determined on an AEI-902 mass spectrometer at the Research Triangle Institute of Mass Spectrometry, Research Triangle Park, NC. Elemental analyses were performed by Desert Analytics, Tucson, AZ.

General Procedure for the Reaction of 4,4-Diethyl-3,5-pyrazolidinedione (1a) with Carboxylic Acid Anhydrides. To a mixture of 4,4-diethyl-3,5-pyrazolidinedione (**1a**)[8] in 50 mL of solvent was added the freshly distilled carboxylic acid anhydride with stirring. The mixture was heated under reflux until most of the insoluble **1a** was consumed. The mixture was cooled to room temperature and filtered to remove either unreacted **1a** or 1-acyl-4,4-diethyl-3,5-pyrazolidinedione (**6**). The filtrate was washed three times with 30-mL portions of 10% Na_2CO_3, dried ($MgSO_4$), and evaporated under reduced pressure to give a mixture of 1,2-diacyl-4,4-diethyl-3,5-pyrazolidinedione (**7**) and unreacted

(12) Attempts to record the ^{15}N NMR spectra of the N-monoacylated products **6** were not successful. This may have been the result of the much lower solubilities exhibited by compounds **6**.

(13) Levy, G. C.; Lichter, R. L. *Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy*; John Wiley and Sons: New York, 1979; chapter 3.

(14) Schuster, I. I.; Dyllick-Brenzinger, C.; Roberts, J. D. *J. Org. Chem.* **1979**, *44*, 1765.

anhydride. The carbonate washings were acidified (HCl) to precipitate the 1-acyl-4,4-diethyl-3,5-pyrazolidinedione (6).

Reaction of 1a with Acetic Anhydride. A. With a Near-Equimolar Quantity of Acetic Anhydride. A mixture of **1a** (9.3 g, 59.6 mmol) and acetic anhydride (10.6 g, 104 mmol) in 50 mL of chloroform was heated at reflux for 1 day. The reaction mixture was filtered to remove 7.24 g (61%) of 1-acetyl-4,4-diethyl-3,5-pyrazolidinedione (**6**, R = Me), mp 168–170 °C. Recrystallization from 95% EtOH gave pure **6** (R = Me) as a white solid: mp 170–172 °C (lit.[8] mp 173–174 °C); IR (Nujol) 3240 (NH), 1750 (C=O), 1715 (sh, C=O), 1700 cm^{-1} (C=O) (lit.[8] 3260 (NH), 1748 (C=O), 1700 cm^{-1} (C=O)); UV (EtOH) λ_{max} 220 nm (ϵ 8420), 255 nm (ϵ 4150) (lit.[8] 219 nm (ϵ 9000), 256 nm (ϵ 4100)); ^1H NMR (400 MHz, acetone-d_6) δ 0.86 (t, 6 H), 1.77 (q, 4 H), 2.50 (s, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 8.94, 23.80, 29.81, 57.15, 163.49, 169.76, 171.49; MS, calcd for $C_9H_{14}N_2O_3$ m/z 198.1004, found m/z, 198.1006; LRMS (relative intensity) m/z, 198 (29), 156 (91), 128 (95), 113 (36), 98 (11), 83 (17), 55 (23), 43 (100), 29 (27). An additional quantity of **6** (R = Me) weighing 3.99 g (94% total yield) was obtained from the acidified sodium carbonate washings.

B. With Excess Acetic Anhydride. A mixture of **1a** (8.43 g, 54 mmol) and acetic anhydride (22.1 g, 217 mmol) in 50 mL of chloroform was heated at reflux for 1 day. No precipitate was present. A quantity of **6** (R = Me) weighing 1.18 g (11%) was obtained from the acidified sodium carbonate washings. The neutral components were distilled to give 9.9 g (76%) of 1,2-diacetyl-4,4-diethyl-3,5-pyrazolidinedione (**7**, R = Me) as a colorless liquid, bp 121–126 °C (1.6 Torr), which solidified on standing; mp 51–56 °C. Recrystallization from 95% EtOH gave pure **7** (R = Me) as a white solid: mp 54–56 °C (lit.[8] mp 54–56.5 °C); IR (Nujol) 1740 (C=O), 1722 cm^{-1} (sh, C=O) (lit.[8] 1748 cm^{-1} (C=O)); UV (EtOH) λ_{max} 215 nm (ϵ 8870) (lit.[8] 217 nm (ϵ 9500)); ^1H NMR (400 MHz, acetone-d_6) δ 0.88 (t, 6 H), 1.90 (q, 4 H), 2.60 (s, 6 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 8.82, 24.40, 29.06, 57.11, 167.46, 171.41; ^{15}N NMR (40.54 MHz, $CDCl_3$) δ 183.7; MS, calcd for $C_{11}H_{16}N_2O_4$ m/z 240.1110, found m/z 240.1112; LRMS (relative intensity) m/z, 240 (7), 198 (67), 156 (100), 128 (85), 113 (2), 98 (10), 83 (11), 55 (18), 43 (91), (10), 83 (11), 55 (18), 43 (91), 29 (22).

Reaction of 1a with Propanoic Anhydride. A. With an Equimolar Quantity of Propanoic Anhydride. A mixture of **1a** (7.06 g, 45.2 mmol) and propanoic anhydride (6.89 g, 45.3 mmol) in 50 mL of chloroform was heated at reflux for 5 days. The reaction mixture was filtered to give 1.09 g of unreacted **1a** (15.4% recovery). The acidified sodium carbonate washings were filtered to yield 5.07 g (53%) of 1-(1-oxopropyl)-4,4-diethyl-3,5-pyrazolidinedione (**6**, R = Et), mp 137–147 °C. Recrystallization from 95% EtOH gave pure **6** (R = Et) as a white solid: mp 151–153 °C; IR (Nujol) 3245 (NH), 1745 (C=O), 1705 cm^{-1} (C=O); UV (EtOH) λ_{max} 220 nm (ϵ 7860), 257 nm (ϵ 3640); ^1H NMR (400 MHz, acetone-d_6) δ 0.86 (t, 6 H), 1.13 (t, 3 H), 1.77 (q, 4 H), 2.93 (q, 2 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 8.34, 8.97, 29.00, 29.81, 57.30, 167.60, 169.81, 171.30; MS, calcd for $C_{10}H_{16}N_2O_3$ m/z 212.1161, found m/z 212.1164; LRMS (relative intensity) m/z, 212 (13), 156 (91), 128 (32), 113 (14), 98 (9), 83 (16), 57 (100), 41 (30), 27 (92). Anal. Calcd for $C_{10}H_{16}N_2O_3$: C, 56.58; H, 7.60; N, 13.20. Found: C, 56.74; H, 7.79; N, 13.20.

B. With Excess Propanoic Anhydride. A mixture of **1a** (6.58 g, 42 mmol) and propanoic anhydride (33.0 g, 254 mmol) in 50 mL of chloroform was heated at reflux for 5 days. No precipitate was present. A quantity of **6** (R = Et) weighing 1.04 g (12%) was obtained from the acidified sodium carbonate washings. The neutral components were distilled to give 3.9 g (34%) of 1,2-bis(1-oxopropyl)-4,4-diethyl-3,5-pyrazolidinedione (**7**, R = Et) as a colorless liquid, bp 82–94 °C (0.12 Torr). Redistillation gave pure **7** (R = Et), bp 84–85 °C (0.12 Torr), which solidified on standing to give a white solid: mp 31–32.5 °C; IR (neat) 1743 cm^{-1} (C=O); UV (EtOH) λ_{max} 216 nm (ϵ 7940); ^1H NMR (400 MHz, acetone-d_6) δ 0.73 (t, 6 H), 1.11 (t, 6 H), 1.76 (q, 4 H), 2.87 (q, 4 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 8.08, 8.58, 28.82, 30.40, 56.97, 168.52, 171.06; ^{15}N NMR (40.54 MHz, $CDCl_3$) δ 185.1; MS, calcd for $C_{13}H_{20}N_2O_4$ m/z 268.1423, found m/z 268.1420; LRMS (relative intensity) m/z, 268 (10), 212 (41), 156 (28), 128 (19), 98 (6), 57 (100), 39 (14), 27 (86). Anal. Calcd for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 58.10; H, 7.51; N, 10.36.

Reaction of 1a with Butanoic Anhydride. A. With an Equimolar Quantity of Butanoic Anhydride. A mixture of **1a** (4.69 g, 30 mmol) and butanoic anhydride (4.74 g, 30 mmol) in 50 mL of chloroform was heated at reflux for 3 days. The reaction mixture was filtered to give 0.77 g of unreacted **1a** (16.4% recovery). The acidified sodium carbonate washings were filtered to yield 4.38 g (65%) of 1-(1-oxobutyl)-4,4-diethyl-3,5-pyrazolidinedione (**6**, R = Pr), mp 121–127 °C. Recrystallization from 95% EtOH gave pure **6** (R = Pr) as a white solid: mp 128–129 °C; IR (Nujol) 3235 (NH), 1747 (C=O), 1703 cm^{-1} (C=O); UV (EtOH) λ_{max} 221 nm (ϵ 8960), 252 nm (ϵ 4110); ^1H NMR (400 MHz, acetone-d_6) δ 0.86 (t, 6 H), 0.96 (t, 3 H), 1.67 (sextet, 2 H), 1.77 (q, 4 H), 2.90 (t, 2 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 8.96, 13.80, 29.00, 38.41, 47.32, 166.70, 169.76, 171.30; MS, calcd for $C_{11}H_{18}N_2O_3$ m/z 226.1317, found m/z 226.1313; LRMS (relative intensity) m/z, 226 (67), 211 (2), 156 (27), 128 (48), 113 (23), 98 (11), 83 (18), 71 (100), 55 (32), 43 (97). Anal. Calcd for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.66; H, 8.17; N, 12.67.

B. With Excess Butanoic Anhydride. A mixture of **1a** (5.61 g, 36 mmol) and butanoic anhydride (34.2 g, 216 mmol) in 50 mL of chloroform was heated at reflux for 5 days. No precipitate was present. A quantity of **6** (R = Pr) weighing 0.015 g (1%) was obtained from the acidified sodium carbonate washings. The neutral components were distilled to give 2.91 g (28%) of 1,2-bis(1-oxobutyl)-4,4-diethyl-3,5-pyrazolidinedione (**7**, R = Pr) as a colorless liquid, bp 85–95 °C (0.05 Torr). Redistillation gave pure **7** (R = Pr): bp 93–94 °C (0.15 Torr); IR (neat) 1745 cm^{-1} (C=O); UV (EtOH) λ_{max} 217 nm (ϵ 8660); ^1H NMR (400 MHz, acetone-d_6) δ 0.89 (t, 6 H), 1.03 (t, 6 H), 1.78 (sextet, 4 H), 1.89 (q, 4 H), 2.96 (t, 4 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 8.65, 13.26, 17.78, 28.92, 38.70, 57.03, 167.64, 171.10; ^{15}N NMR (40.54 MHz, $CDCl_3$) δ 185.7; MS, calcd for $C_{15}H_{24}N_2O_4$ m/z 296.1736, found m/z 296.1740; LRMS (relative intensity) m/z, 296 (2), 226 (19), 156 (8), 128 (9), 98 (3), 71 (100), 55 (31), 43 (11). Anal. Calcd for $C_{15}H_{24}N_2O_4$: C, 60.79; H, 8.16; N, 9.45. Found: C, 60.89; H, 8.43; N, 9.51.

Reaction of 1a with Pentanoic Anhydride. A. With an Equimolar Quantity of Pentanoic Anhydride. A mixture of **1a** (5.14 g, 32.9 mmol) and pentanoic anhydride (6.60 g, 35.5 mmol) in 50 mL of dry 1,2-dimethoxyethane was heated at reflux for 14 days. The reaction mixture was filtered to give 2.09 g of unreacted **1a** (40.7% recovery). The filtrate was evaporated under reduced pressure to give an oily residue. The residue was dissolved in 80 mL of chloroform and extracted three times with 45-mL portions of 10% Na_2CO_3. The carbonate washings were acidified, and the resulting precipitate was filtered to yield 2.69 g (34%) of 1-(1-oxopentyl)-4,4-diethyl-3,5-pyrazolidinedione (**6**, R = Bu), mp 106–113 °C. Recrystallization from 95% EtOH gave pure **6** (R = Bu) as a white solid: mp 117.5–118.5 °C; IR (Nujol) 3215 (NH), 1750 (C=O), 1700 cm^{-1} (C=O); UV (EtOH) λ_{max} 221 nm (ϵ 8550), 254 nm (ϵ 3280); ^1H NMR (400 MHz, acetone-d_6) δ 0.88 (t, 3 H), 0.93 (t, 6 H), 1.40 (sextet, 2 H), 1.65 (pentet, 2 H), 1.79 (q, 4 H), 2.94 (t, 2 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 8.97, 14.01, 22.74, 26.91, 28.97, 36.64, 57.36, 166.88, 169.84, 171.33; MS, calcd for $C_{12}H_{20}N_2O_3$ m/z 240.1474, found m/z 240.1472; LRMS (relative intensity) m/z, 240 (11), 156 (5), 128 (11), 98 (3), 85 (100), 57 (76), 41 (31). Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 60.00; H, 8.54; N, 11.68.

B. With Excess Pentanoic Anhydride. A mixture of **1a** (3.51 g, 25.5 mmol) and pentanoic anhydride (25.15 g, 135 mmol) in 50 mL of chloroform was heated at reflux for 5 days. No precipitate was present. No precipitate of **6** (R = Bu) was obtained from the acidified sodium carbonate washings. The neutral components were distilled to give 1.72 g (21%) of 1,2-bis(1-oxopentyl)-4,4-diethyl-3,5-pyrazolidinedione (**7**, R = Bu) as a colorless liquid, bp 85–105 °C (0.15 Torr). Redistillation gave pure **7** (R = Bu): bp 100–103 °C (0.13 Torr); IR (neat) 1747 cm^{-1} (C=O); UV (EtOH) λ_{max} 217 nm (ϵ 6670); ^1H NMR (400 MHz, acetone-d_6) δ 0.87 (t, 6 H), 0.95 (t, 6 H), 1.44 (sextet, 4 H), 1.73 (pentet, 4 H), 1.89 (q, 4 H), 2.98 (t, 4 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 8.77, 13.58, 21.97, 26.32, 28.98, 36.58, 57.19, 167.98, 171.21; ^{15}N NMR (40.54 MHz, $CDCl_3$) δ 183.2; MS, calcd for $C_{17}H_{28}N_2O_4$ m/z 324.2039, found m/z 324.2044; LRMS (relative intensity) m/z, 324 (4), 240 (25), 156 (8), 128 (7), 98 (3), 85 (100), 55 (11), 39 (34). Anal. Calcd for $C_{17}H_{28}N_2O_4$: C, 62.95; H, 8.70; N, 8.64. Found: C, 62.97; H, 8.69; N, 8.36.

Reaction of 1a with Chloroacetic Anhydride. A. With a Near-Equimolar Quantity of Chloroacetic Anhydride. A mixture of **1a** (5.07 g, 32.5 mmol) and 90% chloroacetic anhydride (7.97 g, 41.9 mmol) in 50 mL of chloroform was heated at reflux for 3 days. The reaction mixture was filtered to give 5.30 g (70%) of 1-(chloroacetyl)-4,4-diethyl-3,5-pyrazolidinedione (**6**, R = CH_2Cl), mp 200–205 °C. Recrystallization from 95% EtOH gave pure **6** (R = CH_2Cl) as a white solid: mp 203–205 °C; IR (Nujol) 3250 (NH), 1750 (sh, C=O), 1715 (C=O), 1670 cm^{-1} (sh, C=O); UV (EtOH) λ_{max} 222 nm (ϵ 5480), 257 nm (ϵ 3510); ^1H NMR (400 MHz, acetone-d_6) δ 0.90 (t, 6 H), 1.82 (q, 4 H), 4.85 (s, 2 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 8.89, 28.96, 44.43, 57.34, 160.04, 169.75, 171.22; MS, calcd for $C_9H_{13}ClN_2O_3$ m/z 232.0615, found m/z 232.0613; LRMS (relative intensity) m/z, 232 (15), 156 (100), 128 (60), 113 (17), 98 (10), 83 (15), 77 (13), 55 (18), 41 (17). Anal. Calcd for $C_9H_{13}ClN_2O_3$: C, 46.46; H, 5.63; Cl, 15.24; N, 12.04. Found: C, 46.59; H, 5.65; Cl, 15.00; N, 12.10. The acidified sodium carbonate washings gave 0.41 g (8%) of **1a**. Evaporation of the chloroform solution gave 3.0 g of a solid–liquid residue. The residue was washed with three 10-mL portions of carbon tetrachloride to yield 0.15 g (2%) of **7** (R = CH_2Cl), mp 82–88 °C.

B. With Excess Chloroacetic Anhydride. A mixture of **1a** (5.23 g, 33.5 mmol) and 90% chloroacetic anhydride (42.60 g, 224 mmol) in 50 mL of chloroform was heated at reflux for 3 days. No precipitate was present. No precipitate was obtained from the acidified sodium carbonate washings. Evaporation of the chloroform solution gave 8.80 g (85%) of 1,2-bis(chloroacetyl)-4,4-diethyl-3,5-pyrazolidinedione (**7**, R = CH_2Cl), mp 86–90 °C). Recrystallization from 95% EtOH gave pure **7** (R = CH_2Cl) as a white solid: mp 91–93 °C: IR (Nujol) 1748 (C=O), 1730 cm^{-1} (C=O); UV (EtOH) λ_{max} 218 nm (ϵ 6920); ^1H NMR (400 MHz, acetone-d_6) δ 0.90 (t, 6 H), 1.96 (q, 4 H), 4.75 (s, 4 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 8.75, 28.96, 43.29, 56.92, 160.97, 170.90; ^{15}N NMR (40.54 MHz, $CDCl_3$) δ 179.2; MS, calcd for $C_{11}H_{14}Cl_2N_2O_4$ m/z 308.0331, found m/z 308.0333; LRMS (relative intensity) m/z 308 (5), 232 (92), 156 (100), 128 (11), 113 (13), 98 (40), 83 (35), 77 (11), 55 (45), 49 (47), 41 (38). Anal. Calcd for $C_{11}H_{14}Cl_2N_2O_4$: C, 42.73; H, 4.56; Cl, 22.94; N, 9.06. Found: C, 42.78; H, 4.63; Cl, 23.11; N, 9.08.

Reaction of 1a with Benzoic Anhydride. A. With an Equimolar Quantity of Benzoic Anhydride. A mixture of **1a** (4.98 g, 31.9 mmol) and benzoic anhydride (8.06 g, 35.7 mmol) in 50 mL of chloroform was heated at reflux for 5 days. The reaction mixture was filtered to give 0.07 g (1.4% recovery) of **1a**. The acidified carbonate washings were filtered to yield 11 g of a white solid. The solid was heated in 300 mL of boiling water and filtered to give 6.17 g (74%) of 1-benzoyl-4,4-diethyl-3,5-pyrazolidinedione (**6**, R = Ph), mp 156–159 °C. Recrystallization from 95% EtOH gave pure **6** (R = Ph) as a white solid: mp 158–160 °C; IR (Nujol) 3138 (NH), 1783 (C=O), 1695 (C=O), 1675 cm^{-1} (C=O); UV (EtOH) λ_{max} 236 nm (ϵ 12500), 270 nm (sh) (ϵ 6470); ^1H NMR (400 MHz, acetone-d_6) δ 0.93 (t, 6 H), 1.80 (q, 4 H), 7.51 (t, 2 H), 7.63 (t, 1 H), 7.75 (d, 2 H); ^{13}C NMR (100) MHz, acetone-d_6) δ 9.11, 29.04, 56.92, 128.74, 130.25, 133.43, 133.73, 163.51, 170.07, 171.36; MS, calcd for $C_{14}H_{16}N_2O_3$ m/z 260.1161, found m/z 260.1164; LRMS (relative intensity) m/z, 260 (3), 105 (100), 98 (1), 77 (46), 51 (10). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.34; H, 6.23; N, 10.83. Evaporation of the chloroform solution gave a mixture containing 1.10 g of neutral components. The mixture was washed with cold low-boiling petroleum ether to yield 0.09 g (2%) of 1,2-dibenzoyl-4,4-diethyl-3,5-pyrazolidinedione (**7**, R = Ph), mp 191–194 °C. Recrystallization from 95% EtOH gave pure **7** (R = Ph) as a white solid: mp 194–196 °C: IR (Nujol) 1780 (C=O), 1746 (C=O), 1710 (C=O), 1690 cm^{-1} (C=O); UV (EtOH) λ_{max} 253 nm (ϵ 19600); ^1H NMR (400 MHz, acetone-d_6) δ 1.01 (t, 6 H), 1.90 (q, 4 H), 7.20 t, 4 H), 7.64 (t, 2 H), 7.98 (d, 4 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 9.13, 29.21, 57.05, 128.22, 130.70, 131.93, 134.12, 164.65, 170.54; ^{15}N NMR (40.54 MHz, $CDCl_3$) δ 170.54; MS, calcd for $C_{21}H_{20}N_2O_4$ m/z 364.1423, found m/z 364.1423; LRMS (relative intensity) m/z, 364 (9), 105 (100), 77 (61). Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.21; H, 5.53; N, 7.69. Found: C, 69.03; H, 5.58; N, 7.72.

Table III. Crystal Data for 6 (R = Me) and 7 (R = Me)

	6 (R = Me)	7 (R = Me)
formula	$C_9H_{14}N_2O_3$	$C_{11}H_{16}N_2O_4$
MW	198.22	240.26
cryst size, mm	0.40 × 0.34 × 0.30	0.72 × 0.35 × 0.30
λ(Cu Kα, Mo Kα), Å	1.541 78	0.710 69
a, Å	6.233 (1)	10.874 (7)
b, Å	11.639 (2)	9.377 (6)
c, Å	13.791 (2)	12.742 (7)
β, deg	91.44 (1)	93.95 (3)
V, Å^3	1000 (2)	1296 (2)
space group	$P2_1/c$	$P2_1/n$
Z	4	4
D_{calc}, g cm^{-3}	1.32	1.23
$F(000)$, e^-	424	512
temp, K	297	297
scan type	$\omega/2\theta$	ω
scan range	2° + dispersion	
scan speed, deg min^{-1}	variable between 4 and 29.3 depending on intensity	
2θ range, deg	$4 \le 2\theta \le 115$	$3 \le 2\theta \le 55$
background	stationary bkgds for 1/2 of scan time on ea side of peak	
octants measd	hkl, hkl	
stds	2 after every 48 reflcns	
no. measd	1431	2985
no. used (NO)	1278	1263
sec. extinction coeff	4 (1) × 10^{-5}	4 (2) × 10^{-5}
μ, cm^{-1}	8.4	0.88
R^a	0.045	0.066
$R_w{}^b$	0.068	0.059
goodness of fit, S^c	1.6	1.7
max shift/θ	0.8	0.6
no. variables (NV)	184	167
diff peak excursion, e Å^{-3}	±0.16	±0.21

$^a R = \sum(||F_o| - |F_c||)/\sum|F_o|$. $^b R_w = [\sum w(||F_o| - |F_c||)^2/\sum w|F_o|^2]^{1/2}$. $^c S = [\sum w(|F_o| - |F_c|)^2/(NO - NV)]^{1/2}$.

B. With Excess Benzoic Anhydride. A mixture of **1a** (6.84 g, 43.8 mmol) and benzoic anhydride (63.88 g, 283 mmol) in 50 mL of chloroform was heated at reflux for 7 days. The precipitate was filtered to yield 3.15 g (20%) of **7** (R = Ph), mp 190–196 °C. No **6** (R = Ph) was obtained from the precipitate isolated from the acidified sodium carbonate washings. The chloroform solution was evaporated under reduced pressure to give a mixture of neutral components. The mixture was washed with low-boiling petroleum ether to produce an additional quantity of **7** (R = Ph) weighing 9.87 g (82% overall yield); mp 188–194 °C.

X-ray Crystallography of 1-Acetyl-4,4-diethyl-3,5-pyrazolidinedione (6, R = Me) and 1,2-Diacetyl-4,4-diethyl-3,5-pyrazolidinedione (7, R = Me). Single crystals of compound **6** (R = Me) were grown by slow evaporation of a saturated solution of **6** (R = Me) in absolute ethanol at room temperature. Single crystals of compound **7** (R = Me) were obtained by recrystallization of **7** (R = Me) from low-boiling petroleum ether. X-ray data for **6** (R = Me) were collected with a crystal mounted on a glass fiber and for **7** (R = Me) with a crystal sealed in a Lindmann glass capillary tube, since **7** (R = Me) was unstable to X-ray exposure in the open atmosphere. Data were collected on a Nicolet R3m/μ diffractometer equipped with a graphite crystal monochromater. Intensities were corrected for background and for Lorentz and polarization effects, but not for absorption. Both structures were solved by direct methods and difference Fourier techniques and refined by the blocked-cascade[15] least-squares refinement technique with Sheldrick's program package SHELXTL[16] for the Data General desktop microeclipse computer. The quantity minimized was $w(|F_o| - |F_c|)^2$, where $w = [1/[\sigma F^2 + gF^2]$; g was 0.0016 for **6** (R = Me) and 0.0002 for **7** (R = Me). The crystallographic data are summarized in Table III.

(15) Sparks, R. A. *Computing Methods and the Phase Problem in X-ray Crystal Analysis*; Pepinsky, R. A., Robertson, J. M., Speakman, J. C., Eds.; Perman Press: New York, 1961; pp 170–187.

(16) SHELXTL Siemens Analytical X-ray Instruments, Inc.: Madison, WI.

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Registry No. **1a**, 4744-72-3; **6** (R = Me), 21769-95-9; **6** (R = Et), 126664-29-7; **6** (R = Pr), 126664-30-0; **6** (R = Bu), 126664-31-1; **6** (R = CH_2Cl), 126664-32-2; **6** (R = Ph), 126664-33-3; **7** (R = Me), 6495-44-9; **7** (R = Et), 126664-34-4; **7** (R = Pr), 126664-35-5; **7** (R = Bu), 126693-72-9; **7** (R = CH_2Cl), 126664-36-6; **7** (R = Ph), 126664-37-7; acetic anhydride, 108-24-7; propanoic anhydride, 123-62-6; butanoic anhydride, 106-31-0; pentanoic anhydride, 2082-59-9; chloroacetic anhydride, 541-88-8; benzoic anhydride, 93-97-0.

Supplementary Material Available: Tables of atomic fractions coordinates, anisotropic thermal parameters, bond distances, and bond angles for **6** and **7** (12 pages); listings of observed and calculated structure factors for **6** and **7** (27 pages). Ordering information is given on any current masthead page.

Practical Synthesis of 5,6,7,8-Tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-5-ol (Cotarnine)

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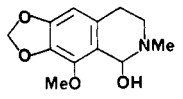
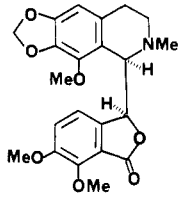
5,6,7,8-Tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-5-ol (cotarnine, **1**), an oxidative degradation product of (3*S*)-6,7-dimethoxy-3-[(5*R*)-5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-5-yl]phthalide (noscapine), has efficiently been synthesized from 2-methoxy-3,4-(methylenedioxy)benzaldehyde (**7**) in 66% overall yield. [*N*-[2-Methoxy-3,4-(methylenedioxy)benzyl]-*N*-methylamino]acetaldehyde dimethyl acetal, obtained by reductive amination of **7** with aminoacetaldehyde dimethyl acetal followed by *N*-methylation, was cyclized in acid to 5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-8-ol (**12**). The major byproduct of the cyclization was C-8 methoxy derivative of **12**, and the amount of this byproduct was decreased by removal of MeOH formed in the reaction mixture. Acetylation of the hydroxyl group in **12** and hydrogenolysis gave 5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinoline (hydrocotarnine), which was oxidized with I_2 followed by basification to afford **1**.

5,6,7,8-Tetrahydro-4-methoxy-6-methyl-1,3-dioxolo-[4,5-*g*]isoquinolin-5-ol (cotarnine, **1**) has been obtained for



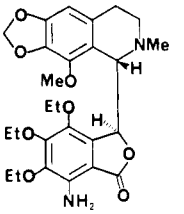
1

the first time by the oxidative degradation of (3*S*)-6,7-dimethoxy-3-[(5*R*)-5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-5-yl]phthalide (noscapine, **2**),[1] which is an isoquinoline alkaloid isolated from



2

opium. Compound **1** shows hemostatic activity and is the key component in the preparation of (3*RS*)-7-amino-4,5,6-triethoxy-3-[(5*RS*)-5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-5-yl]phthalide (tritoqualine, **3**). This is clinically used as an antiallergic drug[2,3]



3

and has recently been shown to have a preventive effect on liver injury in rats induced by treatment with CCl_4 and other biological activities.[4] Clinical consumption of **2** as an antitussive causes a short supply of **2**, and the preparation of **1** from other starting materials is thus desired.

Since Salway's first total synthesis of **1** from amide **4a**,[5] several related syntheses[6-8] have been reported using the Bischler–Napieralski reaction[9] of **4b** and **4c** to construct 3,4-dihydroisoquinolines (Scheme I). In these methods the cyclization reactions can proceed in two directions. For

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