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The Synthesis and Properties of Heterofulvenes, Derivatives of 2,6-Dimethyl-γ-pyrone and -γ-thiapyrone and *N*-Butyl-2,6-dimethyl-γ-pyridone

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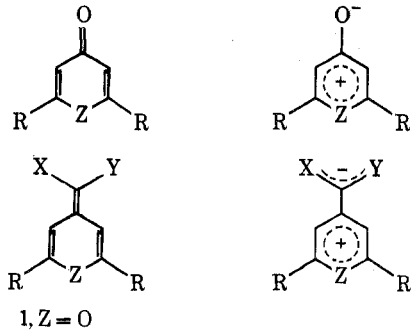
Oxygen-, sulfur-, and nitrogen-containing heterofulvenes, derivatives of 2,6-dimethyl-γ-pyrone (1) and -γ-thiapyrone (2) and *N*-butyl-2,6-dimethyl-γ-pyridone (3), have been prepared, and their properties are reported. The O and S heterocycles were prepared by condensation of 1 and 2, respectively, with active methylene compounds in acetic anhydride. The N heterocycles were obtained from the O heterocycles by reaction with butylamine. Side reactions were observed when butylamine reacted with methyl 2,6-dimethyl-4*H*-pyran-4-ylidenenitroacetate (6) and 2,6-dimethyl-4*H*-pyran-4-ylidenenitroacetone (5). A new convenient route to heterofulvenes which bear a single substituent at the exocyclic double bond was developed. Thus, heterofulvenes substituted by an acetyl group at the exocyclic double bond were found to undergo acetyl cleavage, under very mild acidic conditions, resulting in the formation of monosubstituted heterofulvenes. Deuterium exchange reactions in the systems under consideration were studied. The nmr, uv, and ir data of the disubstituted and monosubstituted heterofulvenes are discussed in terms of the heteroatom and the substituents at the exocyclic double bond.

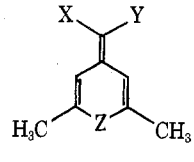
Compounds derived from the formal condensation of γ-pyrones (1), γ-thiapyrones (2), and γ-pyridones (3) with active methylene compounds, having the general structure 4, may be considered as heteroanalogs of heptafulvenes. The literature contains a number of reports on the synthesis and properties of some heterofulvenes and heterofulvalenes derived from γ-pyrones and γ-pyridones.[1] Very little, however, has been published about heterofulvenes derived from γ-thiapyrones (4, Z = S). In this paper we report the synthesis and chemistry of heterofulvenes of type 4; dynamic nmr studies on these compounds will be presented in a later paper.



1, Z = O
2, Z = S
3, Z = N-Bu
4, X, Y = electron-withdrawing groups

Synthesis

The compounds of interest which have been prepared are listed below.



Z = O
5, X = NO_2; Y = $COCH_3$
6, X = NO_2; Y = $COOCH_3$
7, X = NO_2; Y = CN
8, X = $COCH_3$; Y = $COOCH_3$
9, X = $COCH_3$; Y = CN
10, X = $COOCH_3$; Y = CN
11, X = CN; Y = $CONH_2$
12, X = Y = $COCH_3$

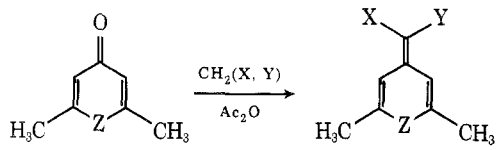
Z = S
13, X = NO_2; Y = $COCH_3$
14, X = NO_2; Y = $COOCH_3$
15, X = NO_2; Y = CN
16, X = $COCH_3$; Y = $COOCH_3$
17, X = $COCH_3$; Y = CN
18, X = $COOCH_3$; Y = CN

Z = *N*-Bu
19, X = NO_2; Y = $COCH_3$
20, X = NO_2; Y = $COOCH_3$
21, X = NO_2; Y = CN
22, X = $COCH_3$; Y = CN
23, X = $COOCH_3$; Y = CN
24, X = CN; Y = $CONH_2$

The oxygen (Z = O) and the sulfur (Z = S) heterocycles were prepared by the condensation of 2,6-dimethyl-γ-pyrone and 2,6-dimethyl-γ-thiapyrone,[3] respectively, with the appropriate active methylene compounds in acetic anhydride (Scheme I). It has previously been reported that the acetic anhydride method is applicable only to those active methylene compounds bearing a nitrile group, but fails with compounds such as acetylacetone and methyl acetoacetate.[4] We have found, however, that this method can be considered to be a general one, inasmuch as, except for 11, all the oxygen and the sulfur analogs could be obtained in this way, although the yields with acetylacetone and methyl acetoacetate were, indeed, very poor. Compound 11 was prepared, as previously reported,[5] by

partial acidic hydrolysis of 2,6-dimethyl-4*H*-pyran-4-ylidenemalononitrile.[6] In the preparation of **7** and **15**, the active methylene compound nitroacetonitrile was generated *in situ*, by dehydration of methazoic acid[7] by the acetic anhydride.

Scheme I

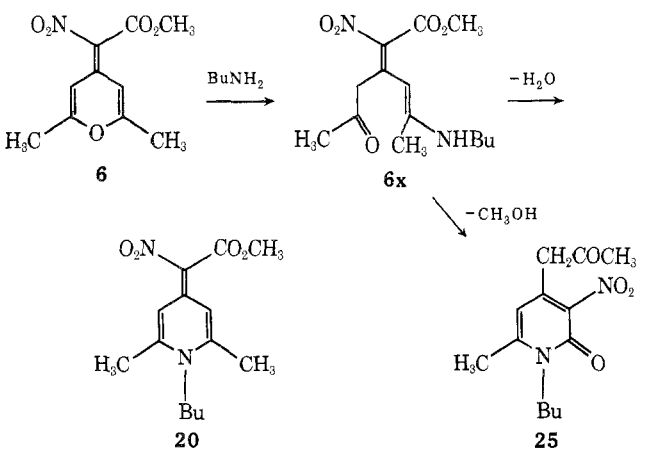


Z = O, S X, Y = electron-withdrawing groups

The nitrogen compounds **19–24** were conveniently prepared from the oxygen analogs by N,O exchange accomplished by heating the latter, either in excess, or with equimolar amounts of butylamine in appropriate solvents.[8] The structures of all the new compounds were confirmed by elemental analysis and spectral methods.

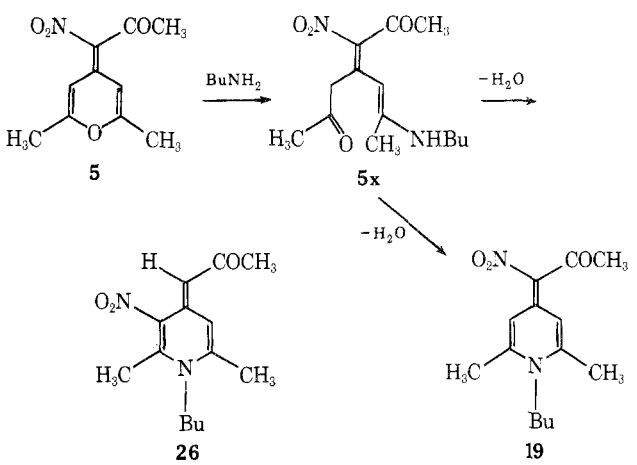
While in most of the cases the reaction with butylamine proceeded satisfactorily, we have encountered two cases in which side reactions took place. When **6** was heated in excess of butylamine at 78°, only one product, mp 127°, was obtained in 34% yield, the physical properties of which were not in accord with structure **20**. This product is considered to be *N*-butyl-3-nitro-4-acetonyl-6-methyl-2-pyridone (**25**), on the basis of spectral data: ir ($CHCl_3$) 1710 (C=O) and 1666 cm^{-1} (CON-Bu); uv λ_{max} (EtOH) 310 nm (ϵ 3300), 370 (3300); nmr ($CDCl_3$) δ 1.03 (3 H, t), 1.60 (4 H, m), 2.26 (3 H, s), 2.44 (3 H, s), 3.66 (2 H, t), 4.02 (2 H, s), 5.94 (1 H, s). The significant features of the nmr spectrum are the two-proton singlet at 4.02 ppm, assigned to $-CH_2COCH_3$, and the presence of only *one* vinylic signal. When the same reaction was carried out in chloroform employing 1 equiv of butylamine, a mixture of **25** and **20**, which could be conveniently separated by crystallization, was obtained. A reaction route that may account for the formation of the two products is presented in Scheme II.

Scheme II



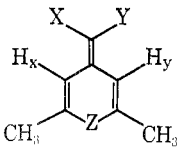
The reaction of **5** in excess butylamine at 78° yielded two structural isomers which were separated by chromatography. One product, obtained in 34% yield, was identified as the corresponding 1,4-dihydropyridine derivative (**19**) on the basis of its elemental analysis and its physical properties. As can be seen (Table I), the chemically nonequivalent protons at positions 3 and 5 of compound **19** exhibit one broad singlet in the nmr spectrum (relative area 2). This observation supports, rather than disproves, structure **19**. The above-mentioned chemical shift equivalency is a consequence of a fast rotation about the exocyclic double bond. This phenomenon was observed in several compounds of type **4** and will be analyzed in a separate publication. The broadening of the vinylic signals was found to be due to allylic type spin coupling with the methyl protons at positions 2 and 6, which was detected in all the compounds of type **4**. The second product, mp 161°, obtained in 30% yield was identified as *N*-butyl-2,6-dimethyl-1,4-dihydropyridine-4-ylideneacetone (**26**). The structural assignment of **26** was based on the following evidence. Elemental analysis was in agreement with the proposed structure; the mass spectrum exhibited a parent peak at *m/e* 264 [mol wt (calcd) 264.33]. The ir spectrum ($CHCl_3$) showed, among others, a conjugated carbonyl band at 1660 cm^{-1}; uv λ_{max} (EtOH) 248 nm (ϵ 6000), 388 (32,700); nmr spectrum ($CDCl_3$) exhibited signals at δ 1.00 (3 H, t), 1.5 (4 H, m), 2.06 (3 H, s), 2.25 (3 H, s), 2.32 (3 H, s), 3.75 (2 H, t), 4.95 (1 H, s, sharp), 8.40 (1 H, s, broad). Although two vinylic-type proton signals are present in the nmr spectrum, this does not support structure **19**, as the signal at δ 4.95, in contrast to the signal at δ 8.40, is very sharp and cannot therefore arise from an allylic coupled proton. The spectrum does, however, support structure **26**, as it is expected that the vinylic proton at the exocyclic double bond would resonate at relatively high field[9] and would not be coupled to the methyl protons. Further information about **26** can be obtained by comparing its nmr data with those of compound **27** (Table I), which was obtained by a different reaction (*vide infra*). Compound **26** is, in fact, a nitro derivative of **27**. This comparison enables us to determine the geometry of **26**. Though **26** can exist in two geometrical isomers, we have isolated only one. On the basis of the similarity in the chemical shifts of the ring proton syn to the acetyl group in **27** (δ 8.27, Table I) and of the ring proton of **26** (δ 8.40), we can safely conclude that structure **26** (Scheme III) correctly describes the geometrical isomer which was isolated. Predomination of this isomer is expected, as this is the thermodynamically more stable one. The reaction pathway which may account for the formation of **19** and **26** from **5** in excess of butylamine is depicted in Scheme III. Initial addition of butylamine and subsequent ring opening lead to the formation of intermediate (**5x**) which possesses two reactive carbonyl groups. Cyclization can therefore take place at either of these carbonyls and thus a mixture of **26** and **19** will result.

Scheme III



The ease with which compounds **5** and **6** tend to participate in competitive modes of cyclization which lead to **26** and **25**, respectively, is attributed to the presence of the strong electron-withdrawing nitro group in the α position

Table I
Nmr Data of Compounds 5–29[a]



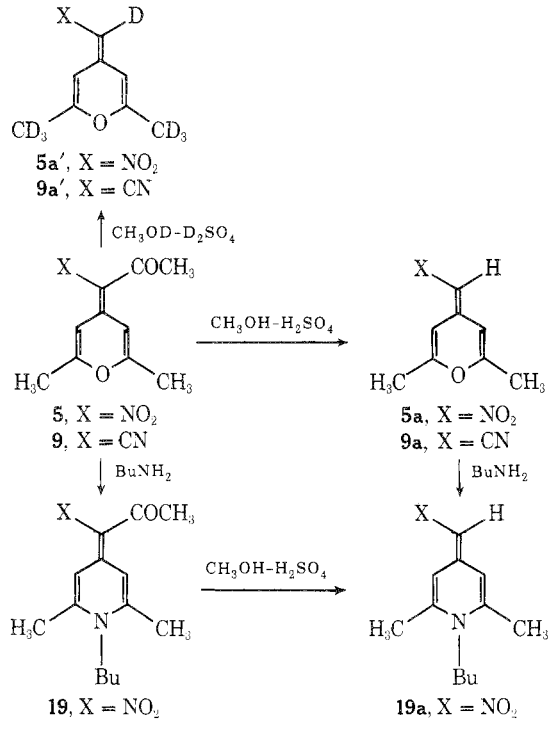
Compd	Yield, %	Mp, °C	Z	X	Y	Chemical shifts in δ ($CDCl_3$) (at ambient temperature) 2,6-Me	H_x	H_y	N-CH_2-	Other groups
5	30	140	O	NO_2	$COCH_3$	2.28	7.10	7.10		$COCH_3$ 2.28
5a	84	105	O	NO_2	H	2.30, 2.32	7.82	5.95		Y = H 6.80
6	34	109	O	NO_2	$COOCH_3$	2.26	7.08	6.60		$COOCH_3$ 3.80
7	8.5	190	O	NO_2	CN	2.48	8.11	6.64		
8	4.5	84	O	$COOCH_3$	$COCH_3$	2.27	6.92	7.32		$COOCH_3$ 3.80, $COCH_3$ 2.20
8a	99	87	O	$COOCH_3$	H	2.10	7.40	5.78		Y = H 4.98, $COOCH_3$ 3.82
9			O	CN	$COCH_3$	2.32	6.58	8.25		$COCH_3$ 2.40
9a	72	94	O	CN	H	2.04, 2.08	6.19	5.77		Y = H 4.19
9a′	81	94	O	CN	D		6.19	5.77		
10	50	178	O	CN	$COOCH_3$	2.29	6.57	7.88		$COOCH_3$ 3.75
11			O	CN	$CONH_2$	2.29	6.62	8.17		$CONH_2$ 5.67
12	1.5	74	O	$COCH_3$	$COCH_3$	2.28	6.95	6.95		$COCH_3$ 2.12
12a	60	85	O	$COCH_3$	H	2.10	7.74	5.76		Y = H 5.35, $COCH_3$ 2.10
13	10	143	S	NO_2	$COCH_3$	2.38	7.71	7.71		$COCH_3$ 2.28
13a	80	83	S	NO_2	H	2.32	8.62	6.54		Y = H 6.94
14	12	116	S	NO_2	$COOCH_3$	2.34	7.50	7.50		$COOCH_3$ 3.79
15	4	216	S	NO_2	CN	2.56	9.04	7.49		
16	0.5	Oil	S	$COOCH_3$	$COCH_3$	2.28	7.52	7.82		$COCH_3$ 2.28, $COOCH_3$ 3.80
17	7	147	S	CN	$COCH_3$	2.44	7.32	9.04		$COCH_3$ 2.44
18	19	185	S	CN	$COOCH_3$	2.42	7.30	8.66		$COOCH_3$ 3.75
19	34	150	*N*-Bu	NO_2	$COCH_3$	2.55	7.94	7.94	4.04	$COCH_3$ 2.49
19a	98	195	*N*-Bu	NO_2	H	2.48	8.30	6.30	3.99	Y = H 6.68
20	32	183	*N*-Bu	NO_2	$COOCH_3$	2.50	7.48	7.48	4.00	$COOCH_3$ 3.83
21	78	263	*N*-Bu	NO_2	CN	2.64	7.50	7.50	4.03	
22	98	178	*N*-Bu	CN	$COCH_3$	2.48	6.80	8.70	3.94	$COCH_3$ 2.34
22a	94	95	*N*-Bu	CN	H	2.30	6.30	5.95	3.68	Y = H 3.75
23	79	135	*N*-Bu	CN	$COOCH_3$	2.43	6.72	8.12	3.90	$COOCH_3$ 3.69
24	62	236	*N*-Bu	CN	$CONH_2$	2.45	6.80	8.47	3.90	$CONH_2$ 5.47
27	70	73	*N*-Bu	$COCH_3$	H	2.32	8.27	6.10	3.75	$COCH_3$ 2.07, Y = H 5.20
28			O	CN	CN	2.34	6.54	6.54		
29			*N*-Bu	CN	CN	2.50	6.70	6.70	3.75	

[a] Satisfactory analytical values (±0.4% for C, H, N, S) for all compounds were reported: Ed.

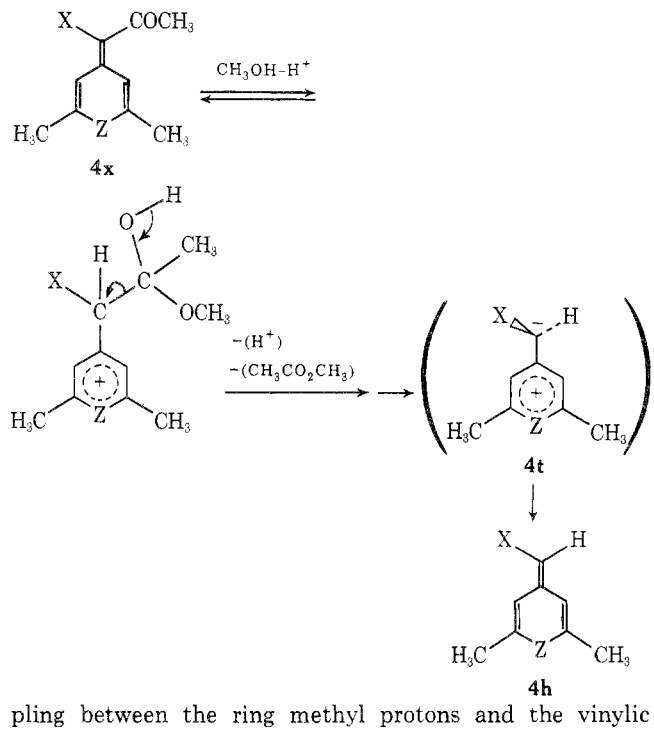
to the acetyl and carbomethoxy groups in these compounds. Thus, the reactivity of these carbonyls toward nucleophilic attack is enhanced, rendering these cyclization routes competitive to the routes leading to **19** and **20**.

Reaction in Acidic Media. The observation that methyl acetoacetate condenses with 2,6-dimethyl-γ-pyrone in poor yield led us to investigate alternative synthetic routes for compound **8**. Specifically, we were interested in finding conditions under which a nitrile group, in this class of compounds, could be transformed into a carbomethoxy group. Thus, heating 2,6-dimethyl-4*H*-pyran-4-ylidenemalononitrile (**28**)[6] in methanol in the presence of 1 equiv of water and a catalytic amount of concentrated sulfuric acid led to the formation of methyl 2,6-dimethyl-4*H*-pyran-4-ylidenecyanoacetate (**10**), identical with the product prepared from methyl cyanoacetate by the acetic anhydride method, as the sole product. When **10** was treated with methanol under the same conditions, no dimethyl 2,6-dimethyl-4*H*-pyran-4-ylidenemalonate was obtained even on prolonged heating, and only starting material was recovered. When 2,6-dimethyl-4*H*-pyran-4-ylidenecyanoacetone (**9**) was subjected to the above reaction conditions, a tlc analysis indicated that the starting material had disappeared completely, and a new spot corresponding to a new product appeared. The isolated product was, however, not the expected **8**, but a new substance to which we have assigned structure **9a** on the basis of the following evidence: the mass spectrum exhibited a parent peak at *m/e* 147 [mol wt (calcd) 147.18]; ir spectrum ($CHCl_3$) showed a conjugated nitrile and double bond stretching bands at 2175 and 1670 cm^{-1}, respectively; the nmr spectrum ($CDCl_3$) showed two methyl signals at δ 2.04 (3 H, s) and 2.08 (3 H, s) and three vinylic signals at 4.19 (1 H, s, sharp), 5.77 (1 H, s, broad), and 6.19 (1 H, s, broad). On repeating the reaction using CH_3OD–D_2O–D_2SO_4, the heptadeuterio derivative (**9a′**) was obtained (Scheme IV), the mass spectrum of which exhibited a parent peak at *m/e* 154, and the ir spectrum ($CHCl_3$) showed additional absorption at 2300 cm^{-1} (C-D). In the nmr spectrum ($CDCl_3$), the methyl signals and the signal at δ 4.19, present in the spectrum of **9a**, were absent. We conclude from these results that under the above reaction conditions the acetyl group at the exocyclic double bond in **9** is cleaved, resulting in the formation of the monosubstituted derivative (**9a**). The sharp high-field vinylic proton signal at δ 4.19 is assigned to the proton at the exocyclic double bond, as was previously argued. The absence of this signal in the deuterio derivative **9a′** supports this assignment.[10] We have found that this "acetyl cleavage" type reaction is common to all acetyl-bearing compounds of type **4** and, in fact, can be carried out under much milder conditions and in the absence of water. Thus, treating a methanolic solution of **5** with catalytic amounts of sulfuric acid at room temperature, resulted in the formation of **5a** (Table I), mp 105°, in 84% yield: mass spectrum *m/e* 167 [mol wt (calcd) 167.17]; ir (KBr) 1670 cm^{-1}; uv λ_{max} (EtOH) 260 nm (ε 5000), 399 (22,200); nmr ($CDCl_3$) δ 2.30 (3 H, s), 2.32 (3 H, s), 5.95 (1 H, s, broad), 6.80 (1 H, s,

Scheme IV



Scheme V



sharp), 7.82 (1 H, s, broad). In CH_3OD-D_2SO_4 the hepta-deuterio compound **5a′** was obtained; the mass spectrum exhibited a parent peak at *m/e* 174 and the ir spectrum (KBr) showed additional absorption at 2330 cm^{-1} (C-D). In the nmr spectrum ($CDCl_3$) of **5a′** the signals at δ 2.30, 2.32, and 6.80 were again missing. Further corroborative evidence for the structures of these deacylated derivatives was obtained from the chemical transformations depicted in Scheme IV. The reaction of **5a** with butylamine afforded **19a**, which was identical with the product obtained by the acetyl cleavage of **19** (which is obtained from the reaction of **5** with butylamine). The monosubstituted heterofulvenes which have been prepared are listed in Table I (see Experimental Section).

By following the progress of the acetyl cleavage using tlc, it was found that the rates were dependent on the nature of the other substituent attached to the exocyclic double bond, as well as on the nature of the heteroatom Z. Thus, in compounds **5**, **8**, **9**, and **12** the rates were enhanced by the presence of the other double bond substituent in the order NO_2 > $COCH_3$ > $COOCH_3$ > CN, which corresponds to the order of the capacity of these groups to stabilize a negative charge. In compounds possessing the same double bond substituents, the dihydropyridines (Z = N-Bu) react faster than the 4*H*-pyrans (Z = O). A tentative mechanism for the deacetylation reaction which accounts for these experimental facts is described in Scheme V.

Assuming that the C-C cleavage step is the rate-determining one, the above qualitative rate orders can now be interpreted in terms of the capacity of X and Z to stabilize the corresponding charges in the transition state leading to **4h**, regardless of whether **4t** describes an intermediate or a transition state.

In view of the mild conditions under which it can be carried out and the excellent yields encountered in most cases, this acetyl cleavage reaction presents an important and facile route to monosubstituted heterofulvenes of type 4 which are not easily accessible by direct routes.[11]

Deuteration. In connection with detailed kinetic nmr studies which are to be carried out on some of the oxygen derivatives, it is necessary to eliminate the allylic coupling between the ring methyl protons and the vinylic protons in positions 3 and 5. To this end, attempts were made to prepare the 2,6-dimethyl-d_6 derivatives of these compounds. Our first approach was to prepare 2,6-dimethyl-d_6-γ-pyrone and condense it with the appropriate active methylene compounds. It has previously been reported that neither the methyl nor the vinylic protons of 2,6-dimethyl-γ-pyrone exchange with deuterium in slightly acidic D_2O solution.[12] In strongly acidic D_2O solutions, exchange occurred mainly at positions 3 and 5 (vinylic protons) and to a lesser extent at the methyls in positions 2 and 6.[13] These results were rationalized in terms of ring opening of the pyrone under strongly acidic conditions, resulting in the formation of a 1,3,5-triketone. Consequently, the more acidic methylene hydrogens exchange faster than the methyl hydrogens. Recyclization, therefore, produces 2,6-dimethyl-γ-pyrone labeled predominantly in the 3 and 5 positions.

In order to minimize the ring opening and thus avoid the exchange of the vinylic protons, we have tried to promote exchange under anhydrous conditions. This was done by treating an anhydrous CH_3OD solution of **1** with D_2SO_4 at room temperature. Under these conditions, however, neither the methyl protons nor the vinylic protons were exchanged with deuterium. Our next approach was to effect the exchange on the heterofulvenes themselves. We have found that the D_2SO_4-CH_3OD method, which failed with 2,6-dimethyl-γ-pyrone, could be successfully applied to some of these compounds. Thus addition of a catalytic amount of D_2SO_4 to a CH_3OD solution of **6**, and maintaining this solution for a few hours at room temperature, resulted in the formation of the corresponding hexadeuterio derivative in a high degree of purity (nmr). Similarly, such exchange could also be performed on the nitrogen analog (**20**). Compound **23**, however, did not exchange deuterium under these conditions. Obviously, such exchange conditions could not be applied to the acetyl-bearing heterofulvenes as they undergo the previously mentioned deacetylation reaction.

Physical Properties

Nmr Spectra. The nmr data of compounds **5**–**24** are summarized in Table I. Protons H_x and H_y are diastereo-

Table II
Electronic and Infrared Spectral Data of Compounds 5–28

Compd	Uv (95% EtOH) λmax, nm			Uv (95% EtOH) ε			Ir (CHCl3), γ, cm⁻¹ C≡C	CN	COCH3	COOCH3
5	260	354	406	5,100	8,600	9,600	1627		1666	
5a	260		399	5,000		22,200	1670[a]			
6	249	330	396	7,000	13,200	11,300	1655			1689
7	260		390	14,350		37,200	1655	2205		
8	247	358		8,300	20,000		1660		1666	1700
8a	231	327		5,000	13,200		1655			1691
9	255	367	381	5,900	24,400	22,600	1622	2177	1666	
9a	227	310		4,900	12,700		1670	2175		
10	248	349	363 sh	6,350	20,200	17,000	1650	2183		1689
12	251	357		7,100	19,300		1630		1655	
12a	244	354		5,900	24,500		1620		1680	
13	270	390 sh	422	6,300	14,300	15,400	1600		1644	
13a							1620			
14	260	363	440	3,600	11,400	9,500	1611			1688
15	274	416 sh	433	13,700	25,800	38,300	1600	2200		
16							1605		1650	1700
17	269	404	423	4,900	28,800	29,600	1600	2180	1649	
18	265	386	405	5,200	37,600	34,400	1605	2177		1683
19	258	330	403	9,900	10,100	16,500	1633		1633	
19a	261		410	2,600		15,200	1635			
20	258		404	10,700		37,400	1627			1711
21	255	277	392	14,400	9,000	43,000	1605	2180		
22	249	374		14,200	39,300		1590	2171	1638	
22a	238	350		1,600	5,400		1640	2160		
23	250 sh	364		4,650	47,000		1611	2161		1656
24		368			40,200		1625	2166		$CONH_2$ 1644
27	250	387		5,000	34,400		1650		1660	
28	255	350		7,200	25,700					

[a] In KBr pellets.

topic and usually give rise to two chemically shifted signals at room temperature which in some compounds are separated by *ca.* 1.5 ppm.[14] The room temperature spectra of **5**, **13**, **14**, **19**, **20**, and **21** exhibit a singlet for $H_x + H_y$. This phenomenon arises from fast thermal isomerization about the exocyclic double bond; at low temperatures, H_x and H_y exhibited chemically shifted singlets. As was previously pointed out, an unambiguous differentiation between the signals of the ring protons (H_x, H_y) and that of the proton at the exocyclic double bond in the monofunctional compounds (**5a**, **8a**, **9a**, **12a**, **13a**, **19a**, **22a**, and **27**; Table I) could be made on the basis of the relative widths of these signals. While the width at half-height of the two signals assigned to the ring protons is in the range of 4–5 Hz, that of the third olefinic signal does not exceed 2 Hz.

A distinction between H_x and H_y could be made on the basis of the following argument. Inspection of the chemical shift data for the N and O series of the *monosubstituted derivatives* reveals that the spectral position of one signal is practically insensitive to the nature of X. This signal was therefore assigned to H_y (Y = H). On the other hand, H_x, being geometrically disposed to the anisotropy effect of X, is shifted by 1.59 (Z = O) and 2.0 ppm (Z = N-Bu) upon changing X from NO_2 to CN. Although H_x and H_y in the *bifunctional* compounds do not resonate at magnetic field values identical with those of H_x in the *monofunctional* compounds, it is assumed that they retain the relative order of the chemical shifts found in the latter group, namely

$$\delta_H(NO_2) \geq \delta_H(COCH_3) > \delta_H(CO_2CH_3) > \delta_H(CN)$$

Such an assumption implies that all factors in a single compound, aside from group anisotropies, affect the chemical shift of H_x and H_y to the same extent. No ambiguities were encountered in our assignments since the differential shifts in all compounds are substantial. Thus, all the assignments in Table I were made on the above basis.

Electronic Spectra. The π–π^* transition maxima of compounds **5**–**27** in ethanol are listed in Table II. A low-wavelength band is present at *ca.* 245–270 nm in the spectra of *all* the compounds in this series (this band is, however, at lower wavelengths in the monosubstituted derivatives). The third band at *ca.* 400 nm in the oxygen and nitrogen heterocycles indicates the presence of a nitro group. Clearly, when comparing compounds with the same X and Y groups the spectra of the S heterocycles are shifted to the red with respect to the O and N analogs. Comparison of the spectra of the latter two groups of compounds indicates that in general the N heterocycles absorb at higher wavelength than the O heterocycles, although some exceptions are noted.

More detailed analysis of the spectra indicated that steric effects play a role in determining the energies and the probabilities of the electronic transitions in some of the compounds. Model examination reveals significant nonbonded interaction between the H atoms at C-3 and C-5 and the X and Y substituents in a planar geometry. Such interaction can be minimized in the monofunctional compounds by adopting the most favorable geometry of the functional group and still keeping this group in the plane of the ring. However, the introduction of a second substituent at the exocyclic double bond restricts the geometrical freedom of the already existing group, since new nonbonded interaction between the two double bond substituents are now generated. This should bring about a larger out-of-plane twist of the two functional groups and should affect the uv spectra. In fact, the above conclusions were reached upon analysis of the relevant spectral data. The longest wavelength high-intensity band should correspond to an electronic transition from the highest occupied MO and is therefore expected to be sensitive to molecular deformation arising from steric interactions. Thus, comparing **12a** with **12** (Table II) reveals a small red shift (3 nm)

of the highest wavelength band, but a 22% *decrease* in the intensity of this band is noted upon the introduction of the second acetyl group. When, however, the highest wavelength bands of **9a** and 2,6-dimethyl-4*H*-pyran-4-ylidenemalononitrile (**28**) (Table II) are compared, it is evident that the introduction of the second cyano group not only produces a pronounced red shift (40 nm) but is also accompanied by an *increase* of over 100% in the intensity of this band. Since the CN group is linear, no steric interactions are generated upon the introduction of the second cyano group and electron delocalization is maximal.

Even more significant is the comparison of the band at the region of 400 nm of compounds **5**, **6**, and **7** with that of **5a**. Thus, upon substituting the exocyclic H of **5a** with acetyl (**5**) and ester group (**6**), the intensity of the above band *diminishes* by 56 and 49%, respectively. However, when a CN group is introduced (**7**), ϵ *increases* by 68%. These results must indicate that while the introduction of the relatively large acetyl and ester groups bring about the said molecular twist, the linear nitrile group does not affect the geometry of the nitro group and allows maximum conjugative interaction of both groups.

Infrared Spectra. The most characteristic ir absorption bands of compounds **5–27** are listed in Table II. It can be seen that, with few exceptions, the stretching frequencies of the exocyclic double bond in the oxygen derivatives **5–12a** fall in the region of 1650–1660 cm^{-1}, those of the nitrogen derivatives **19–27** in the region of 1625–1640 cm^{-1}, and those of the sulfur derivatives in the region of 1600–1610 cm^{-1}. This decrease in the frequency as a function of the heteroatom, which indicates a decrease in the bond strength, or bond order, indicates, in our opinion, that the magnitude of the contribution of a limiting dipolar structure in these series increases in the order of O < N-Bu < S.

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer grating spectrometer, Model 337. Uv spectra were recorded on a Perkin-Elmer 137UV spectrometer. Nmr spectra were taken on a Varian HA-100 spectrometer and on a Jeol JNM-C-60HL spectrometer. Mass spectra were taken with a Hitachi Perkin-Elmer RMU-6 instrument, electron energy 70 eV. Commercial, redistilled malononitrile, methyl acetoacetate, and methyl cyanoacetate were used. Literature procedures were used in the preparation of nitroacetone,[15] methyl nitroacetate,[16] cyanoacetone,[4] and compounds **9**[4] and **11**.[5]

General Procedure for the Preparation of 5, 6, 8, 10, and 12. A solution of 1 equiv (0.01–0.07 mol) of 2,6-dimethyl-γ-pyrone and 1 equiv of the appropriate active methylene compound in Ac_2O (30–100 ml) was refluxed for 2–5 hr. Removal of the Ac_2O at low pressure left a dark tarry residue which was extracted several times with hot ligroin (**5**) or ether (**6**, **8**, **12**). The combined organic extracts were washed with water and dried over $MgSO_4$. Removal of the solvent left a residue which was subjected to column chromatography on Kieselgel (0.05–0.20 mm) employing EtOAc–petroleum ether as eluent. Pure products were obtained in the 10:90 or 20:80 v/v EtOAc–petroleum ether fractions. Compound **10** was obtained by cooling (Dry Ice–acetone) the Ac_2O solution, filtering, and recrystallizing from MeOH.

2,6-Dimethyl-4*H*-pyran-4-ylidenenitroacetonitrile (7). To a solution of 7.69 g (0.062 mol) of 2,6-dimethyl-γ-pyrone in 70 ml of Ac_2O, 6.65 g (0.064 mol) of methazoic acid was added, and the solution was refluxed for 2 hr. Removal of the Ac_2O left a tarry residue which was extracted several times with 60-ml portions of ether. The combined ether solutions were washed with water and dried over $MgSO_4$. Removal of the ether left the product, which was recrystallized from EtOAc.

General Procedure for the Preparation of 13, 14, 15, 16, and 18. A solution of 1 equiv (3–10 mol) of 2,6-dimethyl-γ-thiapyrone and 2 equiv of the appropriate active methylene compound (methazoic acid in the preparation of **15**) in Ac_2O (15–45 ml) was kept at 80–90° for 2–7 hr. Removal of the Ac_2O at low pressure left a residue which was extracted several times with 50-ml portions of ether. The ethereal solution was washed with 15% $NaHCO_3$ solution, then with water, and dried over $MgSO_4$. Removal of the ether left a solid or an oil which was subjected to column chromatography on Kieselgel (0.05–0.20 mm) employing EtOAc–petroleum ether as eluent. Pure products were obtained from the 5:95 or 10:90 v/v EtOAc–petroleum ether fractions.

2,6-Dimethyl-4*H*-thiapyran-4-ylidenecyanoacetone (17). A solution of 1.0 g (0.01 mol) of cyanoacetone (generated by adding 0.01 mol of glacial AcOH to a suspension of 0.01 mol of sodium cyanoacetone enolate in absolute ether and filtering) in 10 ml of absolute ether was added dropwise to a solution of 0.7 g (5.0 mol) of 2,6-dimethyl-γ-thiapyrone in 20 ml of Ac_2O maintained at 90°. After 3 hr at 90°, the reaction mixture was worked up according to the general procedure given above.

General Procedure for the Reaction of $BuNH_2$ with the O Heterocycles. Preparation of 21, 22, 23, and 24. A solution of the respective oxygen derivatives (3–10 mmol) in $BuNH_2$ (6–25 ml) was refluxed for 1–2 hr. Removal of the excess of $BuNH_2$ at low pressure left a solid which was recrystallized from MeOH (**22**, **23**, **24**) or CH_3CN–EtOAc (**21**), affording pure products.

Reaction of Butylamine with 5. A solution of 0.55 g (2.6 mmol) of **5** in 6 ml of $BuNH_2$ was refluxed for 0.5 hr. On keeping the reaction mixture at 0° overnight, a solid separated, which upon filtering afforded 1-*n*-butyl-2,6-dimethyl-1,4-dihydropyridin-4-ylidenenitroacetonitrile (**19**), mp 150° after recrystallization from EtOAc–ligroin. The above filtrate upon evaporation at low pressure afforded a mixture of **19** and *N*-*n*-butyl-2,6-dimethyl-3-nitro-1,4-dihydropyridin-4-ylideneacetone (**26**), which was chromatgraphed on Kieselgel (0.05–0.20 mm), employing EtOAc–petroleum ether as eluent. The 1:3 v/v EtOAc–petroleum ether fraction afforded 176 mg (30%) of **26**: mp 162° after recrystallization from petroleum ether–EtOAc; mass spectrum (%) 264 (100, M^-). *Anal.* Calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.46; H, 7.47; N, 10.47.

1-*n*-Butyl-3-nitro-4-acetonyl-6-methyl-2-pyridone (25). A solution of 0.55 g (4 mmol) of **6** in 5 ml of $BuNH_2$ was refluxed for 5 hr. Upon cooling and maintaining the solution for a few hours in an ice bath, a solid separated and was filtered, affording 0.22 g (34%) of **25**: mp 127° after recrystallization from EtOH; mass spectrum (%) 266 (100, M^+). *Anal.* Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.82; H, 6.79; N, 10.50.

Methyl 1-*n*-Butyl-2,6-dimethyl-1,4-dihydropyridin-4-ylidenenitroacetate (20). A solution of 1.1 g (8 mmol) of **6** and 1 ml (0.01 mol) of $BuNH_2$ in 60 ml of $CHCl_3$ was refluxed for 50 hr. Upon cooling, crystals separated; they were filtered and recrystallized from $CHCl_3$–EtOAc, affording **20**.

Formation of 10 from 2,6-Dimethyl-4*H*-pyran-4-ylidenemalonitrile. To a solution of 0.51 g (3 mmol) of 2,6-dimethyl-4*H*-pyran-4-ylidenemalononitrile in 10 ml of MeOH, 1 ml of water and 1 ml of concentrated H_2SO_4 were added, and the solution was refluxed for 72 hr. On cooling and addition of 100 ml of water, a solid separated and was filtered, affording 0.24 g (39%) of **10**, mp 178° after recrystallization from EtOH. There was no depression of the mixture melting point of **10** prepared from 2,6-dimethyl-γ-pyrone and methyl cyanoacetate and the compound obtained by the present method.

2,6-Dimethyl-4*H*-pyran-4-ylideneacetonitrile (9a). To a solution of 0.38 g (2 mmol) of **9** in 10 ml of MeOH, 1 ml of water and 1 ml of concentrated H_2SO_4 were added, and the solution was refluxed for 24 hr. Upon cooling and addition of ice-cold water, a solid separated and was collected, affording 0.11 g (42%) of **9a**, mp 85–89°. Chromatography on Kieselgel (0.05–0.20 mm), employing EtOAc–hexane as eluent, afforded a pure sample.

A General Procedure for the Cleavage of the Acetyl Group in Acetyl-Bearing Compounds of General Formula 4. A solution of 5 mmol of the appropriate compound in 5 ml of MeOH was treated with 2 drops of concentrated H_2SO_4 at room temperature. The reaction mixture was kept at room temperature until all starting material disappeared (tlc analysis). This usually took 1 hr for the N-Bu derivatives, and up to 96 hr for the oxygen derivatives. The product was isolated by one of the following methods.

Method A. The reaction mixture was cooled in a Dry Ice–acetone bath, whereupon solid separated and was collected by filtration.

Method B. The MeOH was removed at low pressure and the residue dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with 10% $NaHCO_3$ solution, then with water, and dried over Na_2SO_4. Removal of the $CHCl_3$ left a solid that was recrystallized from ligroin.

1-*n*-Butyl-2,6-dimethyl-1,4-dihydropyridin-4-ylideneacetone (27). A solution of 164 mg (1 mmol) of **12a** in 5 ml of $BuNH_2$ was refluxed for 8 hr. The excess of $BuNH_2$ was removed at low pressure and the residue was dissolved in petroleum ether–EtOAc. On cooling (Dry Ice–acetone), 153 mg (70%) of **27** precipitated and as collected by filtration.

Methyl 2,6-Hexadeuteriodimethyl-4*H*-pyran-4-ylidenenitroacetate. To a solution of 215 mg (1 mmol) of **6** in 8 ml MeOD, 4 drops of D_2SO_4 was added, and the solution was kept at 50° for 72 hr. On cooling (Dry Ice–acetone), 200 mg (90%) of product separated and was collected by filtration. The nmr spectrum of the product indicated exchange of about 50% of the methyls' hydrogens by deuterium. The product was redissolved in 8 ml of MeOD containing 4 drops of D_2SO_4, and the reaction mixture was maintained at 50° for an additional 100 hr. Upon cooling, 180 mg (70%) of product was obtained, mp 109°, which was more than 95% hexadeuterated (nmr).

Registry No.—**1**, 1004-36-0; **2**, 1073-80-9; **5**, 49810-66-4; **5a**, 49810-67-5; **6**, 49810-68-6; **7**, 49810-69-7; **8**, 49810-70-0; **8a**, 39588-78-8; **9**, 3280-35-1; **9a**, 49775-27-1; **9a′**, 49810-73-3; **10**, 49810-74-4; **11**, 49810-75-5; **12**, 49810-76-6; **12a**, 39588-76-6; **13**, 49810-78-8; **13a**, 49775-28-2; **14**, 49810-79-9; **15**, 49810-80-2; **16**, 49810-81-3; **17**, 49810-82-4; **18**, 49810-83-5; **19**, 49810-84-6; **19a**, 49810-85-7; **20**, 49775-29-3; **21**, 49810-86-8; **22**, 49810-87-9; **22a**, 49810-88-0; **23**, 49810-89-1; **24**, 49810-90-4; **25**, 49810-91-5; **26**, 49810-92-6; **27**, 49810-93-7; **28**, 28286-88-6; **29**, 49810-95-9; 1-nitro-2-propanone, 10230-68-9; nitromethane, 75-52-5; methyl nitroacetate, 2483-57-0; nitroacetonitrile, 13218-13-8; methyl-3-oxobutyric acid, 105-45-3; methyl acetate, 79-20-9; 3-oxobutyronitrile, 2469-99-0; acetonitrile, 75-05-8; acetonitrile-*d*, 26456-53-1; methylcyanoacetic acid, 105-34-0; 2-cyanoacetamide, 107-91-5; 2,4-pentanedione, 123-54-6; acetone, 67-64-1; malononitrile, 109-77-3; butylamine, 109-73-9; methyl 2,6-hexadeuteriodimethyl-4*H*-pyran-4-ylidenenitroacetate, 49810-96-0.

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Intramolecular Friedel–Crafts Acylation Reaction of 4-Cycloocten-1-yl Acetyl Chloride. A Competitive [$_{\pi}2_s + {}_{\pi}2_a$] Cycloaddition

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The stannic chloride catalyzed intramolecular reaction of 4-cycloocten-1-yl acetyl chloride (**2**) yields the expected Friedel–Crafts type product, *endo*-2-chlorobicyclo[4.2.2]decan-8-one (**5**). The uncatalyzed reaction yields tricyclo[5.3.0.$0^{3,10}$]decan-2-one (**3**) and tricyclo[4.4.0.$0^{3,10}$]decan-2-one (**4**) through a [$_{\pi}2_s + {}_{\pi}2_a$] process.

The fact that a double bond can participate in an intramolecular reaction with a suitably placed cationic center has been known for a long time.[1] The first example of a solvolytic intramolecular cyclization of a simple substituted cycloalkene was reported by LeNy in 1960.[2] Since this report, many papers dealing with intramolecular participation of double bonds in cyclic systems have been published. These papers reported studies on the factors which influence ring closures,[1,3-5] aspects of the π route[6] to classical–nonclassical systems,[7,8] and synthetic routes to otherwise difficultly accessible bicyclic compounds.

The work of Erman and Kretschmar[9] extended the study of ring closures to cases where the cationic center was derived from an acyl chloride group. A number of similar papers have appeared recently[10a,11,12] in which the Friedel–Crafts intramolecular cyclization has led to formation of bicyclic products. The Friedel–Crafts closures to give bicyclic products are of interest for two reasons. First, ring closure affords bifunctional bicyclic products having a ketone and either a halo or olefinic group, while solvolytic ring closures of sulfonate esters, etc., yield monofunctional derivatives. Second, solvolysis of esters derived from alcohols related to the acyl halide may have different selectivities. Thus, 3-(3-cyclohexen-1-yl)-propionyl chloride undergoes an intramolecular ring closure,[10a] but buffered acetolysis of the tosylate of 3-(3-cyclohexen-1-yl)propyl alcohol fails to give cyclization products.[10b]

As part of a study on cationic ring closures of cyclooctenyl derivatives, we investigated the Friedel–Crafts intramolecular acylation reactions of 4-cycloocten-1-yl acetyl chloride (**2**). The stannic chloride catalyzed reaction of **2** gave products expected of a Friedel–Crafts reaction. The uncatalyzed reaction of **2** gave products which arise through the intermediacy of a ketene rather than a cationic intermediate.

Results

4-cycloocten-1-yl acetic acid (**1**) was prepared from 5-bromocyclooctene[13] by malonic ester synthesis. The acid **1** in carbon tetrachloride was converted to the acyl halide **2** with thionyl chloride. Glpc analysis of the product mixture obtained when **2** was heated at reflux in CCl_4 for 7 days showed two compounds (Scheme I) in addition to unchanged starting material. The infrared spectrum of the first unknown compound eluted, **3** (1%), showed no ab-