Photodimeric Cage Compounds. V. Transformations of the Dioximes of the Photodimers of 2,6-Dimethyl- and 2,6-Diethyl-4-pyrone[1,2]

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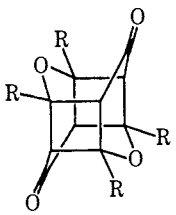
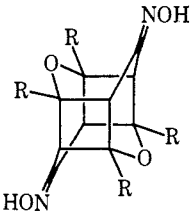
Abstract: Treatment of the dioxime (**3**) of the cage photodimer of 2,6-dimethyl-4-pyrone with concentrated sulfuric acid gives [3-(5-methylisoxazyl]acetone (**5**), the oxime of 2,6-dimethyl-4-pyrone (**12**), and 1,3-dimethyl-2,4-bis-[3-(5-methylisoxazyl)]-1,3-cyclobutanediol (**22**). Catalytic hydrogenation of the cyclobutanediol gives 4-amino-4-{3-[6-(2-hydroxypropyl)-2,4-dimethylpyridyl]}-3-buten-2-one (**30**). Treatment of the dioxime **3** with polyphosphoric acid gives 3,4,6-trimethyl-5-[3-(5-methylisoxazyl)]anthranil (**46**), in addition to **5** and **22**. Treatment of the dioxime (**4**) of the cage photodimer of 2,6-diethyl-4-pyrone with either concentrated sulfuric acid or polyphosphoric acid gives products analogous to **5** and **12** together with the dioxime of the *seco* dimer, formed by simple cleavage of one of the cyclobutane rings of the cage.

The photodimers of 2,6-dimethyl- and 2,6-diethyl-4-pyrone have been shown to have the structures **1** and **2**, respectively.[4,5] During the course of the structural elucidation, the oximes of these compounds, **3** and **4**, were prepared and subjected to strongly acidic conditions in attempts to effect conversion of the ketonic rings of **1** and **2** to lactam rings by Beckmann rearrangement. No reactions of this type were observed, but **3** and **4** underwent a number of interesting acid-catalyzed transformations which we discuss here.



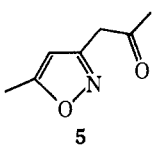
1, R = CH_3
2, R = C_2H_5



3, R = CH_3
4, R = C_2H_5

Brief treatment of the dioxime **3** with concentrated sulfuric acid on the steam bath gave three products: a liquid, A; a crystalline solid, mp 124–124.5°, B; and a crystalline solid, mp 122–122.5°, C. Each of these products was found to have an empirical formula $C_7H_9NO_2$.

Compound A was shown to have the molecular formula $C_7H_9NO_2$. One of its oxygen atoms could be assigned to a nonconjugated methyl ketone function since it showed bands at 5.82 and 7.40 μ in its infrared spectrum, formed a *p*-nitrophenylhydrazone, λ_{max} 250 (ϵ 13,000) and 384 mμ (ϵ 28,000),[6] and gave a positive iodoform test. Bands at 6.22 and 6.77 μ in its infrared spectrum and an ultraviolet maximum at 218 mμ (ϵ 5700) suggested the presence of an aromatic system. These data, the absence of OH and NH stretching bands in its infrared spectrum, and its origin led to its formulation as either the isoxazole **5** or the oxazole **6**. The nmr spectrum of A could be interpreted in terms of either structure; it showed singlets at δ 2.10 (3 H), 2.28 (3 H), 3.78 (2 H), and 6.00 (1 H) ppm, assignable to the protons of the two methyl groups, the methylene group, and the ring of **5** or **6**.



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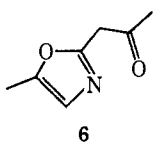

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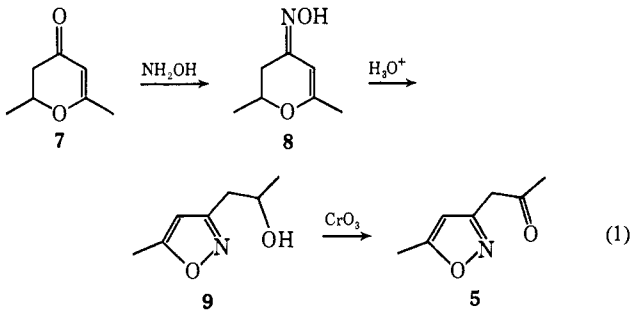
Comparison of the infrared and ultraviolet spectra of compound A with those of 3,5-dimethylisoxazole showed striking similarities; thus the latter showed bands in its infrared spectrum at 6.20 and 6.70 μ, and a maximum in its ultraviolet spectrum at 216 mμ. Further, a series of alkyl-substituted isoxazoles have been reported to have ultraviolet maxima (ϵ 3000–5000) in the 210- to 230-mμ region[7] while neither oxazole[8] nor trimethyloxazole have a maximum in this region. On this basis an independent synthesis of compound **5** was undertaken by the route shown in (1).



(1)

The dihydropyrone **7** was prepared by hydrogenation of 2,6-dimethyl-4-pyrone over palladium on calcium

(1) Paper IV: P. Yates, M. J. Jorgenson, and P. Singh, *J. Amer. Chem. Soc.*, **91**, 4739 (1969).

(2) A preliminary report on this work has been published: P. Yates and E. S. Hand, *Tetrahedron Lett.*, 669 (1961).

(3) (a) Lash Miller Chemical Laboratories, University of Toronto, Toronto, Ontario, Canada; (b) Eastman Kodak Co. Fellow, Harvard University, 1959–1960.

(4) P. Yates and M. J. Jorgenson, *J. Amer. Chem. Soc.*, **85**, 2956 (1963); **80**, 6150 (1958).

(5) P. Yates, E. S. Hand, P. Singh, S. K. Roy, and I. W. J. Still, *J. Org. Chem.*, in press.

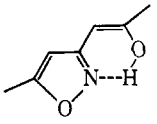
(6) *Cf.* acetone *p*-nitrophenylhydrazone, λ_{max}^{MeOH} 250 (ϵ 11,900) and 390 mμ (ϵ 21,700): F. Bohlmann, *Ber.*, **84**, 490 (1951).

(7) P. Pino, G. Speroni, and V. Fuga, *Gazz. Chim. Ital.*, **84**, 759 (1954).

(8) J. W. Cornforth and R. H. Cornforth, *J. Chem. Soc.*, 96 (1947).

carbonate.[9] Treatment with hydroxylamine hydrochloride and pyridine followed by acidification gave a product with ultraviolet maxima at 218 and 258 mμ. This is considered to be a mixture of the oxime **8** and its rearrangement product, the isoxazole **9**. In one run a small amount of crystalline compound was isolated which is considered to be **8**; it showed infrared bands at 2.78, 3.10 (br), 3.4–4.4, 6.16, and 6.30 μ, and an ultraviolet maximum at 259 mμ (ε 13,000).[10] When the acidified mixture from the reaction of **7** and hydroxylamine was heated, the ultraviolet maximum at 258 mμ disappeared. Work-up of the resulting mixture gave the isoxazole **9**, whose spectra were in excellent accord with this structural assignment (see Experimental Section). Oxidation of **9** with chromic acid gave a product that was found to be identical with compound A, whose structure is thus established as **5**.

It is noteworthy that compound **5** gives positive Tollens and ferric chloride tests and shows a new band at 282 mμ when its ultraviolet spectrum is recorded in basic solution. These observations demonstrate the tendency of **5** to undergo facile enolization in the sense shown in **10**.[11] The major fragment formed from **5** in



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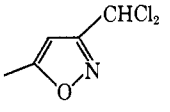

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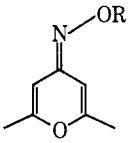
the haloform reaction may also reflect this tendency. Treatment with chlorine and base gave a product that was not obtained completely pure but whose properties showed it to be **11**; this could well be formed *via* chlorination of both the methyl and methylene groups of **5** prior to cleavage.[12]

Compound B was found to be isomeric with compound A (**5**). It showed bands in its infrared spectrum at 2.76, 3.05 (br), 5.90, and 6.14 μ, and an ultraviolet maximum at 261 mμ (ε 15,000). It was soluble in aqueous acid and base, and gave a brown coloration with ferric chloride. Acetylation with acetic anhydride and pyridine gave a monoacetate with a similar ultraviolet spectrum to that of B and bands in its infrared spectrum at 5.70, 5.94, and 6.18 μ. Mild hydrolysis of the acetate regenerated B. These data and its origin led to the formulation of B as **12** and its acetate as **13**. Comparison of the nmr spectrum of **12** with the spectra of 2,6-dimethyl-4-pyrone and the isophorone oximes, **14** and **15**,[13] corroborated this structural assignment (see Table I). The assignments of Page and Jakobsen[13] for **14** and **15** permit the assignment of the lower field vinyl proton signal in the spectrum of B to the olefinic proton having the *syn* relationship to the hydroxyl group of the oxime. The splitting of the methyl proton signal in this spectrum may be due to long-range coupling with the vinyl protons, whose signals are broad; however, it is not excluded that there may be a small chemical-shift difference in the two methyl proton signals. The position of the carbonyl-stretching band in the infrared spectrum of the acetate of B (5.70 μ) also derived analogy from the position of the corresponding band in the spectrum of the oxime acetate **16** (5.70 μ).

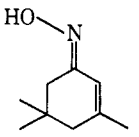
Table I. Nmr Spectral Data for Conjugated Oximes[a]

Compound	δ^{CDCl_3}, ppm =CCH$_3$	=CH	OH
B (**12**)	2.13[b]	5.84,[c] 6.46[c]	9.98
2,6-Dimethyl-4-pyrone	2.18	6.03	
14[d]	1.82	5.88	9.81
15[e]	1.82	6.55	9.78

[a] Singlet signals unless otherwise specified. [b] Doublet (J = 1.5 Hz). [c] Broad. [d] Other signals at δ 0.99 (6 H), 1.93 (2 H), and 2.34 (2 H) ppm. [e] Other signals at δ 0.99 (6 H), 1.93 (2 H), and 2.05 (2 H) ppm.



12, R = H
13, R = COCH$_3$



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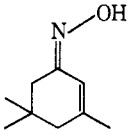

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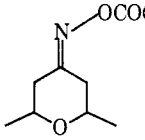

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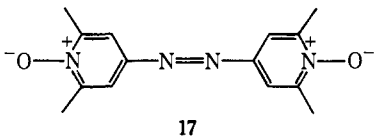

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Confirmation of the assignment of structure **12** to B was obtained in several ways. Treatment of B with hydroxylamine followed by aqueous sodium hydroxide gave an orange product identical with that obtained previously by similar treatment of 2,6-dimethyl-4-pyrone and shown to be **17**.[14] Hydrolysis of B proceeded with great difficulty, however treatment with formaldehyde in boiling aqueous acid solution led to the isolation of 2,6-dimethyl-4-pyrone in low yield. Finally, B was shown to be identical with an authentic sample of **12** prepared by reaction of 2,6-dimethyl-4-thiopyrone with hydroxylamine. Although carbonyl derivatives of several 4-pyrones have previously been prepared *via* the corresponding 4-thiopyrones to avoid the ring-opening reactions that accompany attempted formation of such derivatives from the 4-pyrones themselves,[15] it has been reported that 2,6-dimethyl-4-thiopyrone does not undergo such reaction.[15a] However, we have obtained **12** in 13% yield from its reaction with hydroxylamine. Other products formed in this reaction were 2,6-dimethyl-4-pyrone and the yellow azoxy compound **18**, previously obtained from the reaction of 2,6-dimethyl-4-pyrone with hydroxylamine.[14] Treatment of the mother liquors from the crystallization of **18** with base gave the azo compound **17**, indicating the presence of

(9) *Cf.* J. J. de Vrieze, *Rec. Trav. Chim. Pays-Bas*, **78**, 91 (1959).

(10) The hypsochromic shift of 4 mμ on conversion of **7** to **8** may be compared with the identical shift observed in the case of compounds **55** and **54** (*vide infra*). The isolation of **8** and the observation that it is an intermediate in the formation of the isoxazole favors the assignment to the latter of structure **9**, rather than the structure in which the methyl and 2-hydroxypropyl groups are interchanged.

(11) The fact that **5** gives a positive test with *methanolic* ferric chloride provides evidence for the occurrence of chelation as suggested by the formulation **10**: *cf.* H. Henecka, "Chemie der β-Dicarbonylverbindungen," Springer-Verlag, Berlin, 1950, pp 110–112.

(12) *Cf.* J. Ssuknewitsch and A. Tschilingarjan, *Ber.*, **69**, 1537 (1936).

(13) Data and assignments of T. F. Page, Jr., and R. J. Jakobsen, private communication; *cf.* R. H. Mazur, *J. Org. Chem.*, **26**, 1289 (1961).

(14) P. Yates, M. J. Jorgenson, and S. K. Roy, *Can. J. Chem.*, **40**, 2146 (1962).

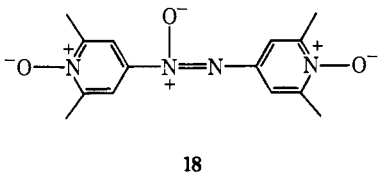
(15) *Cf.*, for example, (a) F. Arndt, E. Scholz, and P. Nachtwey, *Ber.*, **57**, 1903 (1924); (b) A. Hantzsch, *ibid.*, **52**, 1535 (1919).

Table II. Ultraviolet Spectra of β-Amino α,β-Unsaturated Ketones

Compound	R	R′	λ_{max}^{EtOH}, mμ (ε)
D			303,[a] 275[a,b]
D acetate			303 (20,500), 275 (8000)[b]
$CH_3COCH{=}CNR_2$ | R′	H	CH_3 (**23**)	299 (16,000)
	C_2H_5	$CH_2{=}CH$ (**24**)	308 (18,500)[c]
	C_2H_5	$CH_2{=}C(CH_3)$ (**25**)	{310, 315} (30,500)[c]
$C_3H_7COCH{=}CHN(C_2H_5)_2$ | R			307 (28,000), 215 (1200)[c]
$CH_3COC{=}CNCH_2CH_2CN$ | | R′ CH_3	H	H	308 (18,400)[d]
	CH_3	H	306 (22,800)[d]
	H	CH_3	327 (11,200)[d]

[a] Molecular extinction coefficient not recorded since purity not assured. [b] Shoulder. [c] K. Bowden, E. A. Braude, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 45 (1946). [d] N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace, *J. Amer. Chem. Soc.*, **71**, 3337 (1949).

the precursor **19** (or its tautomer).[14] The major product from the reaction of the thiopyrone with hydroxylamine was a compound, $C_{14}H_{18}N_2O_3S$, which is provisionally formulated as the hydrate of the sulfide **20**; on reduction with zinc and acetic acid it gave 2,6-lutidine and on oxidation with hydrogen peroxide gave a product, $C_{14}H_{16}N_2O_4S$, tentatively formulated as the sulfone **21**.



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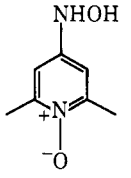

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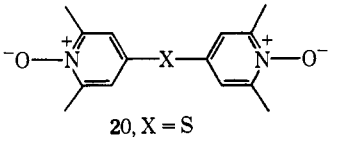
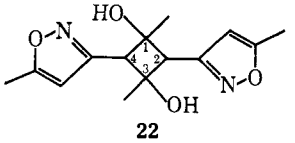


20, X = S
21, X = SO_2

Determination of the molecular weight of compound C by isothermal distillation established its molecular formula as $C_{14}H_{18}N_2O_4$. Comparison of its ultraviolet spectrum [λ_{max} 218 mμ (ε 12,500)] with that of the isoxazole **5** strongly suggested the presence of two isoxazole rings. Its infrared spectrum showed bands at 2.88 and 6.23 μ; the latter was in accord with the presence of the isoxazole rings, and the former indicated the presence of one or more hydroxyl groups. Further, the failure of C to give acetyl or tosyl derivatives indicated that these hydroxyl groups were tertiary. Brief treatment of C with base gave **5** as the only product; heating of C above its melting point or treatment with acid also gave some **5**. These data lead to the formulation of C as the bisisoxazole **22**. This assignment was corroborated by the nmr spectrum of C, which showed



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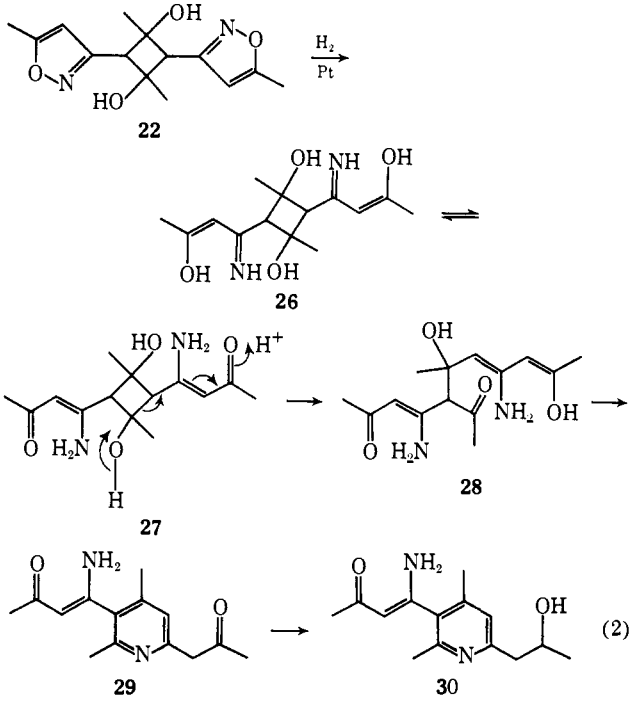
singlets at δ 1.50, 2.40, 3.40, 4.00 (br), and 6.13 ppm with an area ratio of 3:3:1:1:1 that can be assigned to the protons of the C-1 and C-3 methyl, isoxazole methyl, C-2 and C-4 methine, hydroxyl, and isoxazole methine groups, respectively.

Hydrogenation of the bisisoxazole over platinum in acetic acid led to the uptake of *ca.* 4 molar equiv of hydrogen and the formation of an acid-soluble, viscous oily product, D. This was converted by acetic anhydride and pyridine to a crystalline acetate, $C_{16}H_{22}N_2O_3$, which on hydrolysis yielded an oil with spectral properties very similar to those of D, indicating that the latter had been formed from **22** without loss of carbon atoms. Comparison of the ultraviolet spectra of this product and its acetate with those of model compounds (see Table II) suggested the presence of a β-amino α,β-unsaturated ketone grouping (303 mμ) and an aromatic system (275 mμ).

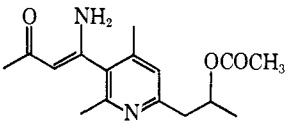
Consideration of possible modes of hydrogenolysis of **22** led to the postulation of the sequence shown in (2) to account for the presence in the hydrogenation



(2)

product of the functional groups suggested by its ultraviolet spectrum. Reductive cleavage of the N–O bonds

of the two isoxazole rings[16] could give the product **26**, which, either prior to or subsequent to tautomerization (*cf.* **27**), could undergo retroaldol cleavage of the cyclobutane ring to give **28** or a tautomer. Cyclization of **28** and dehydration could then give the pyridine **29** which on further hydrogenation could yield **30**. This structure is in accord with the properties of D discussed thus far. It has a pyridine ring, accounting for the basicity of D, and a secondary hydroxyl group which should be readily acetylatable to give **31**, accounting for the formation of the acetate of D. The formula determined for this acetate is that of compound **31**, but since the formation of **30** *via* a sequence of type (2) requires the uptake of only 3 molar equiv of hydrogen, it must be assumed that the observed uptake of *ca.* 4 molar equiv by **22** involves the concomitant formation of more highly hydrogenated products.



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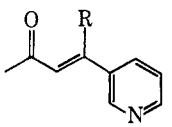
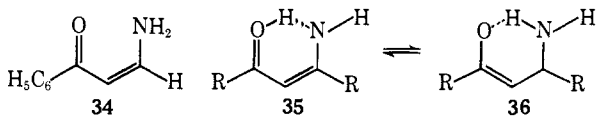


32, R = NH_2
33, R = H

Structure **30** also possesses both the chromophores indicated to be present in D by the ultraviolet spectra. Although these are adjacent in **30**, the spectra of compounds **24** and **25** (see Table II) indicate that replacement of a β-alkyl substituent by an ethylenic double bond has only a small effect on the position of the ultraviolet maxima of β-amino α,β-unsaturated ketones. In order to obtain a more closely related compound for spectroscopic comparison, the pyridine **32** was synthesized by condensing the sodium derivative of acetone with 3-cyanopyridine. This showed in its ultraviolet spectrum maxima at 225 (ε 8000), 248 (ε 6000), and 325 mμ (ε 14,000). Thus, here too the bathochromic shift of the long-wavelength band (26 mμ) relative to the corresponding β-alkyl substituted compound, **23** (see Table II), is unusually small. It may be compared with the bathochromic shift of 36 mμ for compound **33**, λ_{max} 261 mμ, relative to 3-penten-2-one, λ_{max} 225 mμ.[17]



34 **35** **36**

However, the spectrum of **32** is similar to that of the cross-conjugated β-amino α,β-unsaturated ketone **34**, λ_{max} 242 (ε 11,000) and 324 mμ (ε 19,000).[18] The damping of the effect of increased linear conjugation is undoubtedly due to the exceptionally strong conjugative interaction between the unshared pair of electrons on nitrogen and the α,β-unsaturated ketone system.[18] The blurring of the distinction between extension of linear conjugation and cross-conjugation can be interpreted as a consequence of tautomerism between structures of type **35** and **36**. Returning to compound D and its acetate, it may be noted that their long-wavelength maxima show a hypsochromic shift of 22 mμ relative to that of **32**. This can readily be interpreted in terms of steric inhibition of resonance between the pyridine ring and the α,β-unsaturated ketone system. The latter system is flanked in **30** and **31** by two *o*-methyl groups which would be expected to cause a very marked departure from coplanarity of this system and the pyridine ring, thus accounting for the minimal interaction between them.

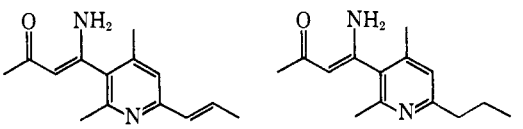
Further evidence can be adduced from several sources in favor of the assignment of structure **30** to compound D. Comparison of the infrared spectra of D and its acetate with those of the related compounds **23** and **32** (Table III) shows striking similarities.[19] The bands at

Table III. Infrared Spectra of Compound D and Related Compounds

Compound	$\lambda_{max}^{CHCl_3}$, μ
D (**30**)	2.88, 2.99, 3.07, 6.18, 6.28, 6.42, 6.58
D acetate (**31**)	2.87, 3.0 (br), 5.79, 6.18, 6.29, 6.42, 6.59
23	2.86, 3.08, 6.16, 6.26, 6.57
32	2.84, 3.05, 6.14, 6.26, 6.40, 6.57

ca. 2.84–2.88 and 3.0–3.1 μ can be assigned to the free and hydrogen-bonded N–H vibrations, respectively, of the primary amino groups. The band at 6.26 μ in the spectrum of **23** is weaker than the bands in the same region in the spectra of the other compounds as expected, since there is overlap in these other cases with bands due to NH deformation and pyridine ring stretching vibrations. The occurrence of the carbonyl-stretching band of the acetate of D at 5.79 μ is in accord with its formulation as an O-acetyl derivative as in **31**.

Treatment of D with concentrated sulfuric acid on the steam bath gave a dehydration product, formulated as **37**. It showed new bands in its infrared spectrum at 6.03 and 10.36 μ, assignable to the stretching and deformation vibrations of the C=C and =CH bonds, respectively, of a *trans*-disubstituted ethylenic double bond. Its ultraviolet spectrum showed maxima at 246 (ε 12,000) and 303 mμ (ε 27,000) in accord with the superimposition of absorption due to the β-amino α,β-unsaturated ketonic system and an alkyl-substituted 2-vinylpyridine system [*cf.* 2-vinylpyridine, λ_{max} 235 (ε 11,500) and 278 mμ (ε 5600)].[20] Hydrogenation of **37** over palladium on charcoal in ethanol gave a dihydro derivative, formulated as **38**. Its ultraviolet spectrum was closely similar to the spectra of **30** and **31**, confirming that the 2-vinylpyridine system of **37** was now absent. This was also evidenced by the absence in its infrared spectrum of bands corresponding to those of **37** at 6.03 and 10.36 μ.



37 **38**

The presence of the pyridine ring in compound D was confirmed by measurement of the pK_a values for the

(16) *Cf.* R. A. Barnes in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1957, p 464.
(17) C. S. Marvel and J. K. Stille, *J. Org. Chem.*, 22, 1451 (1957).
(18) K. Bowden, E. A. Braude, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 45 (1946).
(19) *Cf.* N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace, *J. Amer. Chem. Soc.*, 71, 3337 (1949).
(20) R. P. Mariella, L. F. A. Peterson, and R. C. Ferris, *ibid.*, 70, 1494 (1948).

Table IV. pK_a Values for the Conjugate Acids of Derivatives of Compound D and Related Pyridine Derivatives[a]

Compound	pK_a	ΔpK_a[b]
Pyridine	4.59	
2,6-Lutidine	6.03	+0.72/α-CH_3
2,4,6-Collidine	6.47	+0.44/γ-CH_3
3-Cyanopyridine	2.73	−1.86/β-CN
Dimethyl 3,5-pyridine-dicarboxylate[c]	2.75	−0.92/β-CO_2CH_3
37	4.95	
38	5.35	

[a] Determined in 50% aqueous ethanol by potentiometric titration. [b] Relative to pyridine. [c] Kindly supplied by Dr. J. Kurz.

signals attributable to the pyridine ring proton and the vinylic protons of the propenyl group.

One feature of the chemistry of D remains to be discussed in terms of structure **30**. This concerns its failure to undergo hydrolysis on treatment with dilute hydrochloric acid at room temperature for 3 hr. Such resistance is most unusual for β-amino α,β-unsaturated ketones, which are normally susceptible to very ready hydrolysis to the enols of β-diketones.[19,23] This lack of reactivity in the present case can be ascribed to steric hindrance. As discussed earlier, the two methyl groups in the *ortho* relationship to the β-amino α,β-unsaturated

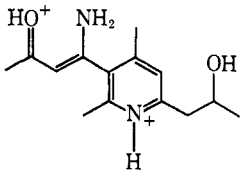
Table V. Nmr Spectra of Derivatives of Compound D and Related Compounds[a]

Compound	δ^{CDCl_3}, ppm: $CH_3C=$	CH_3CO	γ-$ArCH_3$	α-$ArCH_3$	COCH=	β-ArH	NH_2
37	1.90[b]	1.98	2.25	2.40	5.00	6.65[c]	10.00
38[d]		1.95[e]	2.28[e]	2.45[e]	4.88	6.68	9.28[f] 6.18[f]
2,4,6-Collidine			2.15	2.40		6.80	
23	1.88	1.98			5.16[g]		9.78[f] 6.75[f]
$(CH_3COCH{=}CNHCH_2)_2$[h] (with CH_3)	1.91	1.99			4.99		10.13
32		2.05			5.35	7.14[i]	9.50[f] 6.75[f]

[a] All signals are singlets unless otherwise specified and have relative areas in accord with the assignments. [b] Doublet, J = 6 Hz. [c] Complex multiplet which also includes signals due to vinylic protons of the propenyl group. [d] Triplet, J = 6 Hz, at δ 0.93 ppm. [e] The multiplets due to the methylene groups fall under these peaks. [f] Approximate center of broad band. [g] Doublet, J = 1 Hz. [h] G. O. Dudek and R. H. Holm, *J. Amer. Chem. Soc.*, **83**, 2099 (1961). [i] Doublet of doublets, J = 5 and 8 Hz; other ring proton signals at δ 7.75 (m), 8.43 (dd, J = 1.5 and 5 Hz), and 8.63 (d, J = 1.5 Hz) ppm.

conjugate acids of its dehydration product (**37**) and the hydrogenation product (**38**) of the latter. Determination of these pK_a values and those of model compounds by potentiometric titration in 50% aqueous ethanol gave the results shown in Table IV. The values found for the transformation products of D are readily interpreted in terms of the additive effect of the substituents[21] in structures **37** and **38**, with alkyl groups exercising a base-strengthening effect and the vinyl and β-amino α,β-unsaturated ketone groups exercising a base-weakening effect as expected. The effect of the noncoplanar β-amino α,β-unsaturated ketone group is intermediate between the effects of coplanar methyl ester and nitrile groups.

Strong corroborative evidence for the structural assignments made for D and its congeners derives from nmr studies. Comparison of the nmr spectra of compounds derived from D with those of related compounds is made in Table V, which also gives proposed assignments. The NH_2 protons frequently give rise to very broad signals. One of these signals appears in the δ 9–10-ppm region and is assigned to the proton involved in intramolecular hydrogen bonding; the other NH_2 proton gives rise to a signal at higher field (δ 6–7 ppm),[22] In the case of **37**, the latter signal is superimposed on the ketone function in **30** may be expected to cause a marked departure from coplanarity of this function and the pyridine ring. The approach of water at the β-carbon required to effect hydrolysis must occur approximately orthogonally to the plane of the unsaturated ketone function. Because this plane makes a considerable dihedral angle with the plane of the ring, such approach of water will be severly impeded by the *o*-methyl groups. This interpretation is, of course, analogous to that long accepted to explain the resistance of the carbonyl carbon of acetomesitylene to nucleophilic attack.[24] Another factor contributing to the resistance of **30** to hydrolysis is the presence of the basic pyridine function; protonation of this undoubtedly takes precedence over protonation of the much more weakly basic β-amino α,β-unsaturated ketone function. Thus the protonation of the latter that is required to initiate acid-catalyzed hydrolysis will require the formation of the unfavorable dication **39**. Another case in which both



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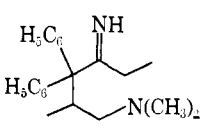

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(21) *Cf.* H. C. Brown, D. H. McDaniel, and O. Häfliger in "Determination of Organic Structures by Physical Methods," Vol. 1, E. A. Braude and F. C. Nachod, Ed., Academic Press, New York, N. Y., 1955, p 567; J. Shorter and F. J. Stubbs, *J. Chem. Soc.*, 1180 (1949).

(22) G. O. Dudek and R. H. Holm, *J. Amer. Chem. Soc.*, **83**, 2099 (1961).

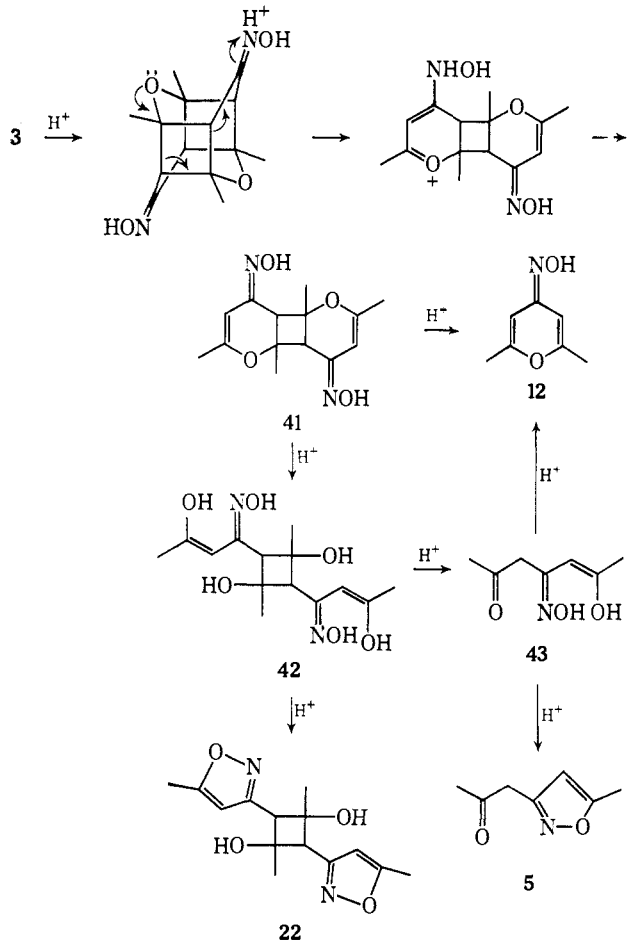
(23) L. Claisen, *Ber.*, **24**, 3900 (1891); E. Fischer and C. Bülow, *ibid.*, **18**, 2131 (1885).

(24) R. G. Kadesch, *J. Amer. Chem. Soc.*, **66**, 1207 (1944).

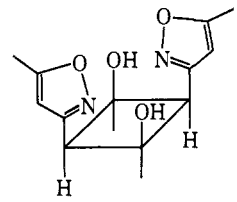
steric and electrostatic factors are most probably involved is that of the ketimine **40**, whose hydrolysis requires heating in a sealed tube with hydrochloric acid,[25]

We return now to the consideration of the origin of the three products A(**5**), B(**12**), and C(**22**) from the cage dioxime **3**. A reaction sequence that accounts for their formation is presented in Scheme I. The first

Scheme I



step, the acid-catalyzed cleavage of one of the cyclobutane rings of the cage dioxime to give the dioxime **41**, finds close analogy in the acid-catalyzed cleavage of the photodimers **1** and **2** to diketones corresponding to **41**,[5,26] The further acid-catalyzed cleavage of the remaining cyclobutane ring to give the oxime **12** also is analogous to reactions observed in the photodimer series to give the parent pyrones.[4,5] Acid-catalyzed cleavage of the enol ether groups of **41** would give rise to **42**,[27] which by acid-catalyzed isoxazole ring closure would give **22**.[28] An acid-catalyzed retroaldol cleavage of the cyclobutane ring of **42** would give **43**, which could serve as the source of the keto isoxazole **5**. It also might provide an alternative route for the formation of **12**. Although the bisisoxazole **22** is readily converted to **5** on treatment with base, and also gives some **5** under certain acidic conditions, it was found to be unaffected by the conditions used in the acid treatment of **3**, and thus cannot be considered to be an intermediate in the formation of **5** from **3**. Also, the possibility that **5** might be formed from **12** *via* **43** was excluded by the demonstration that **12** is unchanged under these acid conditions. This scheme leads to the assignment of the stereochemistry shown in **44** for the bisisoxazole. This is based on the assumption that no epimerization has occurred during its formation from **41**, a view which appears reasonable since the formation of the intermediates required for such epimerization would be expected to lead to cleavage of the cyclobutane ring.



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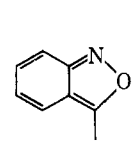
The failure to observe products derived by Beckmann rearrangement on treatment of **3** with concentrated sulfuric acid led to an investigation of its behavior under different acidic conditions. Hot polyphosphoric acid was chosen for this purpose since it has been used previously to effect the conversion of oximes to amides in cases where other acidic reagents have led to alternative reactions.[29] However, in the case of **3**, again no Beckmann rearrangement products could be detected. The major products were **5** (52%) and **22** (37%); none of the pyrone oxime **12** was obtained, but two new, minor products were isolated, only one of which, E, was obtained in sufficient amount to permit its identification.

Compound E was a crystalline solid, mp 109.5–110.5°, shown to have the molecular formula $C_{14}H_{14}N_2O_2$. It showed in its infrared spectrum bands at 6.10, 6.24, and 6.37 μ and in its ultraviolet spectrum a series of bands between 260 and 290 mμ, a maximum at 318 mμ (ϵ 6100), and very high end absorption. The close similarity of this latter spectrum with that of 3-methylanthranil, **45** (see Figure 1), strongly suggested the presence of an anthranil ring system. These observations together with the origin of E led to its formulation as **46**. This structural assignment was fully sup-



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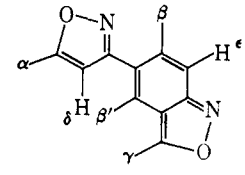


46

ported by comparison of the nmr spectrum of E with the spectra of **45**, **5**, and **22** (Table VI). Signals at δ 2.30 (3 H) and 5.98 (1 H) ppm can be assigned to the methyl and ring protons, respectively, of the isoxazole ring in analogy to the assignments for **5** and **22**, while signals at δ 2.83 (3 H) and 7.10 (1 H) ppm can be assigned to the five-membered ring methyl protons and the six-membered ring proton, respectively, of the anthranil system in analogy with the spectrum of **45**. The remaining signals, δ 2.08 (3 H) and 2.48 (3 H) ppm, are assigned to

(25) M. Bockmühl and G. Ehrhart, *Ann.*, **561**, 52 (1949).
(26) D. J. MacGregor, Ph.D. Thesis, University of Toronto, 1967.
(27) Since the reaction medium is concentrated sulfuric acid, it is probable that **42** and **43** are not present as such, but are formed as their bisulfates.
(28) Reference 16, p 454; *cf.* the formation of **9** from **8**.
(29) *Cf.* F. D. Popp and W. E. McEwen, *Chem. Rev.*, **58**, 321 (1958); F. Uhlig and H. R. Snyder in "Advances in Organic Chemistry: Methods and Results," Vol. 1, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, New York, N. Y., 1960, p 65.

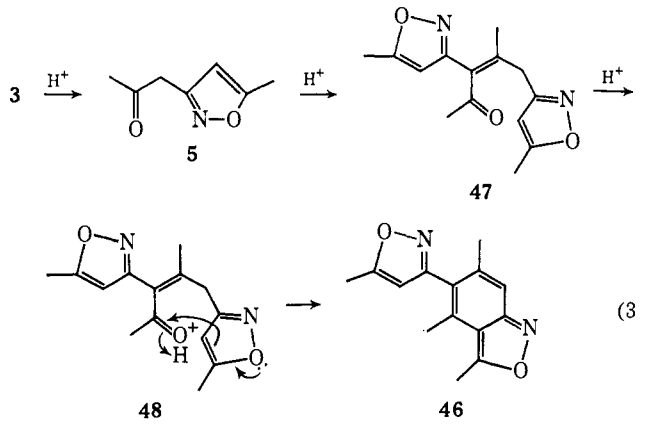
Table VI. Nmr Spectra of Compound E and Related Compounds[a,b]

Compd	α	δ^{CDCl_3}, ppm β,β′	γ	δ	ε
E (46)	2.30	2.08,2.48	2.83	5.98	7.10
45			2.73		7.25[c]
5[d]	2.28			6.00	
22[d]	2.40			6.13	

[a] All signals are singlets unless otherwise specified and have relative areas in accord with the assignments. [b] For designation of assignments see 46. [c] Multiplet. [d] Only relevant signals listed.

the protons of the six-membered ring methyl groups of the anthranil system. The former of these appears at unexpectedly high field, presumably as a result of shielding by the isoxazole ring which must lie considerably out of the plane of the anthranil ring system because of steric interactions with the adjacent methyl groups (*vide supra*). The lower field position of the signal assigned to the second of these methyl groups can be interpreted as due to the counteracting deshielding effect of the other, coplanar five-membered ring.

One possible course for the formation of **46** in the reaction of **3** with polyphosphoric acid is shown in (3). This involves an aldol self-condensation of the keto isoxazole **5** followed by dehydration to give **47**. Electrophilic substitution at C-4 of an isoxazole ring as in **48** would then lead to **46**. The efficiency of polyphosphoric acid as a cyclodehydrating reagent is well



(3

known[29] and isoxazoles are known to be susceptible to electrophilic attack at the 4 position.[30] The plausibility of sequence (3) is strengthened by the observation that treatment of **5** with polyphosphoric acid also gives **46**. However, it is possible that in the case of its formation from **3**, the main reaction path proceeds *via* the bisisoxazole **22**, although this was not itself isolated as a product in the reaction with polyphosphoric acid. Retroaldol reaction of this could lead to the formation of **47** and thence to **46** as in (3).

Treatment of **4**, the dioxime of the cage photodimer, **2**, of 2,6-diethyl-4-pyrone, with concentrated sulfuric acid gave four products. The major product is a liquid assigned the keto isoxazole structure **49** on the basis of analogy of its spectra and other properties (see Experimental Section) with those of the keto isoxazole **5** obtained from **3**. Another, isomeric, solid product, mp

(30) *Cf.*, for example, A. Quilico and C. Musante, *Gazz. Chim. Ital.*, 71, 327 (1941); A. Quilico and R. Justoni, *ibid.*, 70, 3 (1940).

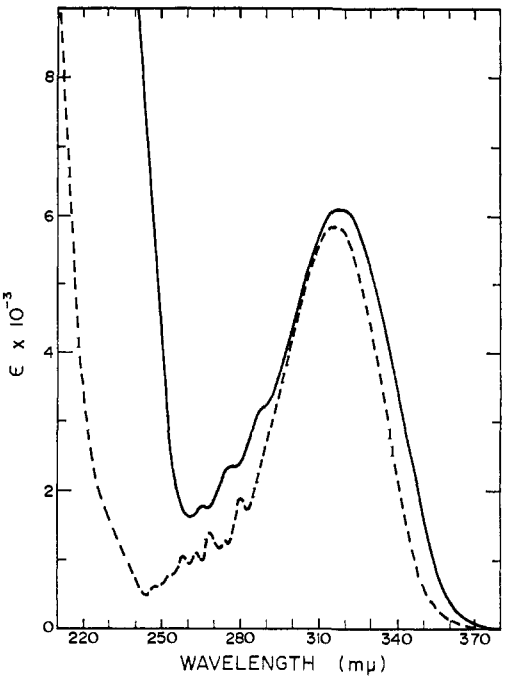
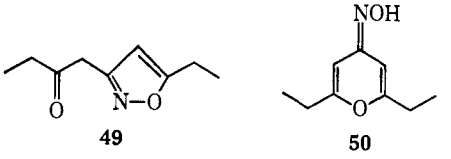
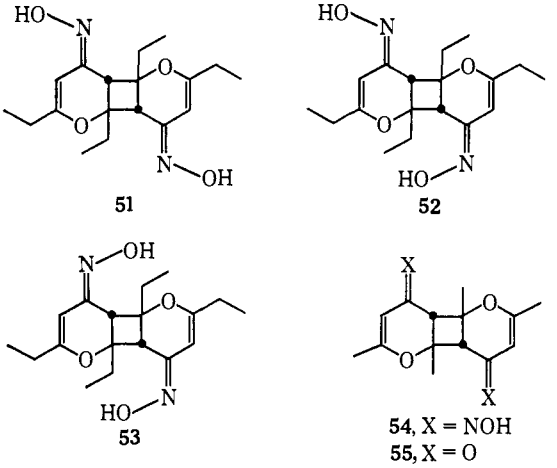


Figure 1. Ultraviolet spectra in ethanol; – – –, 3-methylanthranil (**45**); ———, compound E (**46**).

69.5–70.5°, could be assigned the pyrone oxime structure **50** for similar reasons (see Experimental Section). No product analogous to the bisisoxazole **22** was isolated in this case.

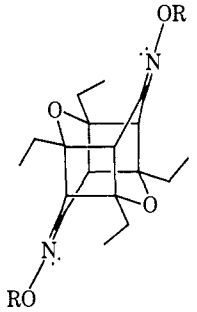


The other products, F and G, were high-melting crystalline, isomeric compounds, mp 192.5–193 and 212° dec, respectively, and were assigned the molecular formula $C_{18}H_{26}N_2O_4$. They both had bands in their solution infrared spectra at 2.77, 3.05 (br), and 6.1 μ, but their absorption in the fingerprint region differed. Their ultraviolet maxima were also very similar: λ_{max} 263 mμ (ε 34,000) and 264 mμ (ε 33,600), respectively. These data led to the assignment to them of two of the three stereoisomeric structures **51–53**. This assign-

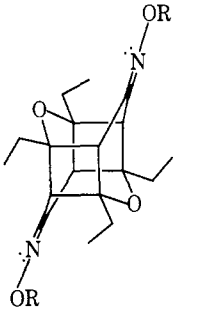


ment was buttressed by the preparation of **54**, a dioxime of the *seco* dimer **55** obtained on cleavage of one of the cyclobutane rings of the cage photodimer **1**,[4,26] and the demonstration that its ultraviolet spectrum, λ_{max}^{EtOH} 262 mμ (ε 29,200), is very similar to the spectra of F and G. No evidence is available that permits assignment of individual structures to F and G.

The isolation of stereoisomeric dioximes in this case raises the question of the stereochemical homogeneity of the dioximes of the cage photodimers themselves. The dioxime **4** can exist in two stereoisomeric forms, **56** and **57**. Indeed, acetylation of **4** with acetic anhydride



56, R = H
58, R = $COCH_3$



57, R = H
59, R = $COCH_3$

and pyridine led to the isolation of two diacetates which differed in their melting points and solubilities, and in the fingerprint regions of their solution infrared spectra, but had identical nmr spectra.[31] Hydrolysis of the individual diacetates returned samples of dioxime whose infrared spectra also differed slightly in their fingerprint regions.[32] The less soluble diacetate, mp 219–222° dec, is tentatively assigned the centrosymmetric structure **58**, while the more soluble diacetate, mp 170–171°, is assigned the less symmetrical structure **59**. This evidence that the dioxime **4** consists of a mixture of the stereoisomers **56** and **57** does not permit, however, a correlation with the formation of the stereoisomeric dioximes F and G, for it is probable that the original stereochemical differentiation will be lost in the course of the acid-catalyzed transformation.

The formation of the dioximes F and G by the acid-catalyzed transformation of **4** lends considerable strength to the reaction sequence postulated in Scheme I to account for the products obtained from **3**, although the reason for the failure to isolate the analogous dioximes (**41**) in that case is not clear. The failure to isolate an analog of the bisisoxazole **22** from **4** can be attributed to increased steric interactions in the already crowded molecule **22** (*cf.* **44**) or its precursor **42**, leading to more ready cleavage of the cyclobutane ring. Treatment of **4** with hot polyphosphoric acid gave rise to the same products as were obtained from its reaction with sulfuric acid. The formation of an analog of the anthranil **46** was not observed in this case, a circumstance that again can be attributed to steric factors.

Experimental Section

Melting points and boiling points are uncorrected. Solutions in organic solvents were dried over anhydrous sodium sulfate.

Dioxime of the Photodimer of 2,6-Dimethyl-4-pyrone (3). The photodimer **1**[4] (9.00 g, 0.036 mol) and hydroxylamine hydrochloride (11.5 g, 0.166 mol) were added to pyridine (100 ml) and absolute ethanol (100 ml), and the mixture was heated under reflux on the steam bath for 5 hr. The solution was concentrated under reduced pressure until crystallization began, and water (*ca.* 150 ml) was added until no further precipitation occurred. The yield of product was quantitative (10.0 g). Four crystallizations from pyridine–water and heating for 24 hr at 80° (0.3 mm) afforded the hemihydrate of **3**; this began to turn brown at 275° and decomposed at 305° (evacuated capillary); λ_{max}^{Nujol} 3.10, 3,20, and 6.00 μ.

Anal. Calcd for $C_{14}H_{18}N_2O_4 \cdot 0.5H_2O$: C, 58,52; H, 6.67; N, 9.75. Found; C, 58.77; H, 6.58; N, 10.24.

The water of hydration could not be removed completely by heating the sample for 8 days at 100° (0.3 mm), but an anhydrous sample was obtained after four crystallizations from large volumes of dry acetonitrile; λ_{max}^{Nujol} 3.05 and 6.10 μ; λ_{max}^{EtOH} 232 mμ (ε 17,300).

Anal. Calcd for $C_{14}H_{18}N_2O_4$; C, 60.42; H, 6.52. Found: C, 60.42; H, 6.48.

Treatment of 3 with Sulfuric Acid. Formation of Compounds A–C (5, 12, and 22). The recrystallized, air-dried dioxime **3** (6.8 g) was added in portions to concentrated H_2SO_4 (25 ml); the warm solution was heated on the steam bath for 13 min, cooled under running cold water, and poured onto ice. A small amount of a dark brown, tarry substance separated and was removed with a stirring rod. Aqueous 5 *N* sodium hydroxide (150 ml) was added with stirring and thorough cooling. Scratching or seeding caused the precipitation of almost pure compound C (2.10 g, 30%), which was filtered. One crystallization from benzene–petroleum ether (bp 30–60°) gave colorless needles (1.80 g), mp 121–122°. If the dark brown substance was not removed, compound C could be purified only by chromatography. The filtrate was neutralized by further addition of aqueous 5 *N* sodium hydroxide and then extracted five times with chloroform (total, 650 ml). The extract was dried and stripped of solvent to give a yellow oil (2.9 g). Further addition of aqueous 5 *N* sodium hydroxide to pH 11 followed by extraction yielded a further quantity of oil (1.0 g). The infrared spectra of the oils were similar.

The oils from several preparations were combined with the residue from the mother liquors of the crystallization of compound C (12.5 g) and chromatographed on alumina (Woelm, neutral, grade 3, 300 g), in benzene. Elution with benzene gave a brown liquid (1.96 g), which on molecular distillation (80°, 0.8 mm) gave compound A as a colorless liquid. Further elution with benzene and with 2, 5, and 10% ether in benzene afforded compound C (4.39 g), mp 120–121.5° after one crystallization from benzene–petroleum ether. Elution with 25% and 50% ether in benzene gave compound B (1.77 g), which after crystallization from benzene–petroleum ether had mp 111–120°.

Compound A (5) was purified by three molecular distillations (70–80°, 0.8 mm); λ_{max}^{neat} 3.18, 5.82, 6.22, 6.77, and 7.40 μ; λ_{max}^{EtOH} 218 mμ (ε 5700); δ^{neat} 2.10 (s, 3), 2.28 (s, 3), 3.78 (s, 2), and 6.00 (s, 1).

Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07; mol wt, 139, Found; C, 60.50; H, 6.46; N, 10.00; mol wt [Rast (exaltone)], 150.

Compound A deposited silver with Tollen's reagent, gave a green color with ferric chloride in methanol, and formed iodoform when treated with sodium hydroxide and iodine. It was recovered unchanged after treatment with 10% hydrochloric acid on the steam bath for 30 min.

The *p*-nitrophenylhydrazone of A was prepared by the method of Shriner and Fuson,[33] two recrystallizations from benzene–petroleum ether gave yellow needles, mp 125–126°; λ_{max}^{EtOH} 218 (inflection, ε 14,500), 250 (ε 13,000), and 384 mμ (ε 28,000).

Anal. Calcd for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.15; N, 20.43. Found; C, 57.08; H, 5.27; N, 20.79.

Compound B (12) was purified by rechromatography on alumina (Woelm, grade 3, neutral) in benzene. Elution with benzene and 25% ether in benzene gave needles which after three recrystallizations from benzene–petroleum ether had mp 124–124.5°; $\lambda_{max}^{CHCl_3}$ 2.76, 3.05 (br), 5.90, and 6.14 μ; λ_{max}^{EtOH} 261 mμ (ε 15,000); δ^{CDCl_3} 2.13 (d, J = 1.5 Hz, 6), 5.84 (br s, 1), 6.46 (br s, 1), and 9.98 (s, 1).

Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.63; H, 6.53; N, 10.35.

(31) Only a single diacetate was isolated from similar acetylation o the dioxime **3**.

(32) The differences in the case of the dioxime samples were smaller than in the case of the acetates; furthermore, the distinction must be considered less decisive in any event since the spectra were taken in the solid state.

(33) R. L. Shriner and R. C, Fuson, "The Systematic Identification of Organic Compounds," 3rd ed, John Wiley & Sons, Inc., New York, N. Y., 1948, p 171.

Compound B was recovered unchanged from a solution in concentrated sulfuric acid that had been heated on the steam bath for 6 min.

Compound C (22) was obtained after four recrystallizations from benzene–petroleum ether as flat needles, mp 122–122.5°; λ_{max}^{Nujol} 2.81, 2.86, 3,17, and 6,25 μ; λ_{max}^{EtOH} 218 mμ (ϵ 12,500); δ^{CDCl_3} 1,50 (s, 6), 2.40 (s, 6), 3.40 (s, 2), 4.00 (s, 2), and 6.13 (s, 2).

Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07; mol wt, 278. Found: C, 60,51; H, 6,55; N, 10.29; mol wt, 250 (isothermal distillation).

Compound C did not react with 5% bromine in carbon tetrachloride, but decolorized 2% potassium permanganate in aqueous acetone. With ferric chloride in methanol, it gave a green color which slowly changed to brown and then red. It did not form a *p*-toluenesulfonate with *p*-toluenesulfonyl chloride in pyridine at room temperature.

Warming of compound C with aqueous 10% sodium hydroxide on the steam bath for 5 min resulted in a pale yellow solution. This was extracted with ether, and the extract was dried and stripped of solvent to give a liquid that was identified as compound A by infrared spectral comparison.

Gentle heating of compound C above its melting point for 5 min also resulted in the formation of compound A as indicated by comparison of infrared spectra.

Treatment of compound C with conc sulfuric acid on the steam bath for 10 min gave a dark solution from which only starting material (94%) could be isolated. When compound C (0.25 g) was heated on the steam bath for 40 min with aqueous 5% hydrochloric acid (4 ml) and methanol (5 ml) followed by removal of most of the methanol, an oil was formed that solidified on cooling. The solid (0.12 g), mp 120–121.5°, was shown to be starting material by spectral comparison. The filtrate was neutralized and extracted twice with chloroform. The pale yellow liquid (0.13 g) remaining after removal of solvent from the extract was shown to be compound A by infrared spectral comparison.

3,5-Dimethylisoxazole was prepared by the method of Lampe and Smolińska.[34] A mixture of hydroxylamine hydrochloride (8.0 g, 0,115 mol) and potassium carbonate (8.0 g, 0.058 mol) was added in portions to acetylacetone (8.0 g, 0.080 mol). The mixture was boiled under reflux for 4 hr and allowed to stand overnight. Water and chloroform were added, the layers were separated, and the aqueous layer was extracted again with chloroform. The combined chloroform extracts were dried and stripped of solvent and the product was distilled to give 3,5-dimethylisoxazole as a colorless liquid (4.3 g, 55%); bp 139–141° [lit.[34] bp 56–57° (27 mm)]; λ_{max}^{neat} 6.20, 6.70, 6.86, 7.08, 7.31, and 7.97 μ.

2,4,5-Trimethyloxazole was prepared by an adaptation of the procedure reported by Wiley.[35] A mixture of alanine (20.0 g, 0.22 mol), acetic anhydride (92 ml, 1 mol) and pyridine (92 ml) was heated on the steam bath for 24 hr. After about 30 min, the alanine had dissolved to give a yellow solution and a gas (presumably carbon dioxide) was evolved. The solvents were distilled at 40 mm, and the residue was distilled at 1 mm to give **3-acetamido-2-butanone** (17,9 g, 62%), as a colorless liquid, bp 93–94.5° (1 mm) [lit.[35] bp 104–110° (2–3 mm)]. This product (10.0 g, 0.078 mol) was added to concentrated sulfuric acid (32 ml) over a period of 10 min, when heat was evolved and the solution became yellow. The solution was warmed on the steam bath for 20 min, cooled, and poured onto crushed ice. The mixture was neutralized with aqueous 25% sodium hydroxide, and extracted with chloroform. The extract was dried and distilled through a Vigreux column to give 2,4,5-trimethyloxazole as a colorless liquid (total, 6.1 g, 70%) in two fractions, bp 75–127 and 127–130° (lit.[35] bp 132–133°). The infrared spectra of the fractions were the same; λ_{max}^{neat} 2.95, 6.05, 6.32, 6.43, 6.99, 7.25 (sh), 7.58, and 7.88 μ.

The **picrate of 2,4,5-trimethyloxazole** was prepared by adding the oxazole (0.55 g, 1.0 mmol) to a warm solution of picric acid (1.15 g, 1.0 mmol) in 95% ethanol (20 ml). When the mixture was cooled and scratched, the picrate separated as yellow needles (0.65 g, 38%), which after one recrystallization from 95% ethanol had mp 110–112° (lit.[35] mp 110.5–112.5°). The picrate was decomposed in warm methanolic solution by the addition of aqueous ammonium hydroxide. The product had an infrared spectrum identical with that reported above for 2,4,5-trimethyloxazole.

Hydrogenation of 2,6-Dimethyl-4-pyrone. Formation of 7 and 2,3,5,6-Tetrahydro-2,6-dimethyl-4-pyrone.[9,36] 2,6-Dimethyl-4-pyrone (40 g) and 10% palladium–calcium carbonate (27 g) were added to methanol (300 ml) and the mixture was shaken under hydrogen for 22 hr in a Parr apparatus at an initial hydrogen pressure of 49 psi. The solids were filtered and rinsed thoroughly with methanol. The washings were added to the filtrate and most of the methanol was evaporated under reduced pressure. The residue was taken up in chloroform and extracted three times with 6 *N* hydrochloric acid (50-ml portions) to remove unconsumed pyrone. The chloroform layer was washed with water, dried, and stripped of solvent to give a liquid, which was fractionally distilled under reduced pressure. Two fractions were collected; 2,3,5,6-tetrahydro-2,6-dimethyl-4-pyrone (15 g), bp 50–51.5° (3.5 mm) [lit.[9] bp 80° (32 mm)] and 2,3-dihydro-2,6-dimethyl-4-pyrone (**7**) (4.6 g, 11%), bp 80–82° (3.5 mm) [lit.[9] bp 85–86° (14 mm)]. The dihydropyrone fraction showed hydroxyl absorption in its infrared spectrum. It was chromatographed on alumina (Woelm, grade 1, neutral); elution with benzene–petroleum ether gave **7**; λ_{max}^{neat} 6.01 and 6.22 μ.

The tetrahydropyrone fraction was purified by chromatography on alumina (Woelm, grade 1, neutral) in petroleum ether. Elution with this solvent gave the tetrahydropyrone as a colorless liquid;[37] λ_{max}^{neat} 5.68 (sh), 5.80, and 5.90 μ (sh); no high intensity ultraviolet absorption >210 mμ.[38]

3-(2-Hydroxypropyl)-5-methylisoxazole (9). The purified dihydropyrone **7** (3.2 g, 25 mmol) was dissolved in a mixture of pyridine (20 ml) and absolute ethanol (20 ml). Hydroxylamine hydrochloride (2.0 g, 29 mmol) was added, and the mixture was boiled under reflux on the steam bath for 2 hr. The solution was concentrated to small volume (*ca.* 5 ml), acidified with dilute hydrochloric acid to pH 1, and extracted twice with chloroform (50-ml portions). Evaporation of the chloroform left an oil (2.9 g), λ_{max}^{EtOH} 218 and 258 mμ, indicating that it was a mixture of the dihydropyrone oxime **8** and the isoxazole **9**.

The oxime could be partially extracted from a chloroform solution of the crude product with aqueous 10% sodium hydroxide. Acidification of the extract with dilute hydrochloric acid followed by extraction with chloroform gave a semisolid residue from which **8** was isolated by crystallization from methanol–ether. Two further crystallizations from the same solvent pair and one from chloroform–ether afforded a small amount of needles, mp 130–130.5°; $\lambda_{max}^{CHCl_3}$ 2.78, 3.10 (br), 3.4–4.4, 6.16, and 6.30 μ; λ_{max}^{EtOH} 259 mμ (ϵ 13,000). Attempts to repeat the isolation of **8** failed.

The residues from the mother liquors from the crystallization of the oxime were added to the impure isoxazole **9**, obtained by evaporation of the chloroform solution of the original crude product after extraction with base. The mixture was dissolved in ethanol, acidified to pH 3, and heated on the steam bath for 30 min, when its ultraviolet spectrum indicated that virtually all of the oxime **8** present had been converted to **9**. The solution was diluted with water and extracted three times with chloroform (20-ml portions). Evaporation of the solvent gave an orange oil (1.8 g), which was purified by molecular distillation (70°, 0.5 mm) to give **9** as a colorless liquid; λ_{max}^{neat} 2.95, 3.18, and 6,22 μ; λ_{max}^{EtOH} 216 mμ (ϵ 4600); δ^{CDCl_3} 1.20 (d, J = 6 Hz, 3), 2.33 (s, 3), 2.72 (d, J = 5 Hz, 2), 4.09 (m, 1), 4.35 (s, 1), and 5.97 (s, 1).

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.40; H, 8.03; N, 10.16.

Oxidation of 9. Formation of 5. Chromium trioxide (0.50 g, 50 mmol) was partially dissolved in glacial acetic acid (15 ml) and the hydroxyisoxazole **9** (0.50 g, 3.5 mmol) was added. The mixture was heated on the steam bath and allowed to stand overnight. The resulting deep blue solution was poured into water, and the mixture was extracted five times with chloroform (total, 100 ml). The extract was washed with dilute aqueous potassium carbonate, dried, and stripped of solvent to give **5** as a liquid (0.28 g, 57%), which was purified by chromatography on alumina (Woelm, grade 3, neutral) with elution with benzene. The spectra of this compound were identical with those of compound A.

The ***p*-nitrophenylhydrazone of 5,** prepared as in the case of compound A, had mp 125.5–126.5°, undepressed on admixture with the *p*-nitrophenylhydrazone of compound A.

Reaction of 5 with Sodium Hypochlorite. Formation of 11. Compound A (0.78 g, 5.6 mmol) was dissolved in a solution of

(34) W. Lampe and J. Smolińska, *Roczniki Chem.*, 28, 163 (1954); *Chem. Abstr.*, **49**, 8922 (1955).

(35) R. H. Wiley, *J. Org. Chem.*, **12**, 43 (1947).

(36) The hydrogenation of 2,6-dimethyl-4-pyrone to give 7 has subsequently been investigated in more detail.[26]

(37) This is probably the *cis* isomer; *cf.* J. J. de Vrieze, *Rec. Trav. Chim. Pays-Bas*, **66**, 486 (1947).

(38) This product has previously been reported[9] to have λ_{max} 276 mμ (ϵ 3700), perhaps due to contamination with 2,4-pentanedione.

sodium hydroxide (1.5 g) in water (10 ml). Clorox[39] (30 ml, 23.5 mmol NaOCl) was added to the solution in small portions with swirling and cooling. The solution immediately became cloudy and an oil separated. The mixture was allowed to stand for 10 min, and the oil was then removed with a medicine dropper, taken up in chloroform, and dried. Removal of the solvent left a fragrant liquid (0.57 g, 60%), which was purified by two molecular distillations (45°, 0.4 mm) to give **11** as a colorless liquid; λ_{max}^{neat} 3.18, 6.23, 12.70, and 13.15 μ; λ_{max}^{EtOH} 223 mμ (ϵ 4500). Compound **11** gave no coloration with ferric chloride in methanol. A satisfactory elemental analysis was not obtained.

Acetylation of Compound B (12). Formation of 13. Pyridine (3 ml) and acetic anhydride (3 ml) were added to compound B (0.120 g). The solution was heated on the steam bath for 1 hr and then stripped of solvent. The solid residue was taken up in benzene and chromatographed on alumina (Woelm, grade 3, neutral, 7 g). Elution with benzene gave **13** (0.100 g, 64%), mp 127–129°. Treatment in chloroform with Norit followed by three recrystallizations from benzene–petroleum ether gave colorless needles, mp 128.5–129.5°; $\lambda_{max}^{CHCl_3}$ 5.70, 5.94, 6.18, and 6.37 μ; λ_{max}^{EtOH} 214 (ϵ 7500) and 266 mμ (ϵ 16,900).

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73; mol wt, 181. Found: C, 59.87; H, 6.05; N, 7.46; mol wt (Rast), 179.

Treatment of a methanolic solution of **13** with aqueous 5% hydrochloric acid on the steam bath for 10 min regenerated **12**, as shown by spectral comparison.

2,3,5,6-Tetrahydro-2,6-dimethyl-4-pyrone oxime was prepared from the tetrahydropyrone (*vide supra*) by the method of Borsche and Thiele.[40] After sublimation it had mp 89–90° (evacuated capillary) (lit.[40] mp 82–83°); λ_{max}^{Nujol} 2.97 and 6.03 μ.

Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.47; H, 9.21; N, 9.66.

2,3,5,6-Tetrahydro-2,6-dimethyl-4-pyrone oxime acetate (16) was prepared by treating the oxime with acetic anhydride and pyridine on the steam bath for 90 min. Removal of the solvents and molecular distillation (60–70°, 0.3 mm) of the residual mobile yellowish liquid gave **16** as a colorless liquid; λ_{max}^{neat} 5.68 and 6.09 μ.

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.46; H, 8.31; N, 7.48.

Reaction of Compound B (12) with Hydroxylamine. Formation of 17. Compound B (50 mg, 0.36 mmol) was heated with hydroxylamine hydrochloride (50 mg, 0.72 mmol) in pyridine (2 ml) and absolute ethanol (2 ml) on the steam bath for 3 hr. The solution was concentrated to dryness, and water (*ca.* 0.5 ml) was added to the residue. On addition of aqueous 10% sodium hydroxide (*ca.* 0.75 ml), the solution immediately turned red, and orange needles separated. The crystals were filtered, washed with water and recrystallized from ethanol–water to give **17**, identified by infrared and ultraviolet spectral comparison and mixture melting point with an authentic sample.[14]

Hydrolysis of Compound B (12). Formation of 2,6-Dimethyl-4-pyrone. Compound B (70 mg) was added to water (2 ml) containing conc sulfuric acid (two drops) and formaldehyde (aqueous 37%, 2 ml), and the solution was boiled under reflux for 24 hr. After neutralization with aqueous 10% sodium hydroxide, the brown solution was extracted five times with chloroform. The extract was dried and stripped of solvent to give a thick orange oil (80 mg) from which an amorphous white solid was obtained by sublimation. This was dissolved in chloroform, and the solution was extracted three times with 8 *N* hydrochloric acid. The extract was neutralized with solid sodium carbonate and extracted with chloroform. The chloroform extract was dried and stripped of solvent. The residue was sublimed, and the sublimate was chromatographed on alumina (Woelm, grade 3, neutral) in benzene. Elution with 10% ether in benzene gave 2,6-dimethyl-4-pyrone, mp 130–133°, identified by infrared and ultraviolet spectral comparison and mixture melting point with an authentic sample.

Treatment of compound B with either dilute or concentrated hydrochloric acid on the steam bath for 2 hr failed to effect hydrolysis.

2,6-Dimethyl-4-thiopyrone was prepared by the method of Hantzsch.[41] Samples from different preparations had mp 143–144°, 148–149°, and 150–151° (lit.[41] mp 145°), but their spectra were indistinguishable; $\lambda_{max}^{CHCl_3}$ 6.02 (sh), 6,08, and 6.37 μ; λ_{max}^{EtOH} 254 (ϵ 8500) and 341 mμ (ϵ 21,000); δ^{CDCl_3} 2.22 (s, 6) and 6.80 (s, 2).

Reaction of 2,6-Dimethyl-4-thiopyrone with Hydroxylamine. Formation of 2,6-Dimethyl-4-pyrone, 12, 17, 18, and 20. 2,6-Dimethyl-4-thiopyrone (2,00 g, 14,3 mmol) was heated with hydroxylamine hydrochloride (1.00 g, 14.4 mmol) and sodium carbonate (1.00 g, 9.5 mmol) in absolute ethanol (25 ml) on the steam bath for 20 hr. The solution was cooled, twice its volume of water was added, and the pH was adjusted to 6 with 5% hydrochloric acid. The solution was extracted three times with chloroform (total, 120 ml), and the extract was dried and stripped of solvent. The residue was slurried with benzene, and the slurry was placed on a column of alumina (Woelm, grade 3, neutral, 60 g). Elution with benzene gave unconsumed thiopyrone (0.15 g, 9%). Elution with 5% and 10% ether in benzene gave 2,6-dimethyl-4-pyrone (0.17 g, 10%), which after three crystallizations from benzene–petroleum ether had mp 131–133°.

Elution with 25% and 50% ether in benzene gave a pale yellow substance (0.21 g, 13%), which after recrystallization from benzene–petroleum ether and treatment with Norit gave **12**, mp 122–123°. This was shown to be identical with compound B by infrared and ultraviolet spectral comparison and mixture melting point.

Elution with 50% chloroform–ether gave **20** (0.75 g, 46%), as a colorless solid, mp 205–206° dec. After four crystallizations from chloroform–ether, it had mp 202–203° (evacuated capillary); λ_{max}^{Nujol} 2.93, 3.03, 6.00, 6.22, 6.45, 8.07, and 8.12 μ; λ_{max}^{EtOH} 221 (ϵ 37,600), 287 (ϵ 28,500), and 315 mμ (ϵ 18,700).

Anal. Calcd for $C_{14}H_{16}N_2O_2S \cdot H_2O$: C, 57.13; H, 6.17; N, 9.52; S, 10.87. Found: C, 57,17; H, 6.22; N, 9.77; S, 11.02.

Compound **20** was soluble in 5% hydrochloric acid, methanol, and hot chloroform, insoluble in benzene, petroleum ether, ether, and aqueous 5% sodium hydroxide, was stable to dilute acid and base (in ethanol) on the steam bath for 1 hr, gave a negative ferric chloride test, and did not precipitate lead sulfide from aqueous lead acetate.

Elution with 10% methanol in chloroform gave a brown oil (0.35 g) which on standing deposited crystals. This crude product had ultraviolet maxima at 217 and 278 mμ. On attempted crystallization from ethanol–water yellow needles began to deposit after 2 days. Recrystallization from the same solvent mixture gave **18**, identified by infrared and ultraviolet spectral comparison with an authentic sample.[14] Treatment of the mother liquor from the first crystallization with aqueous 10% sodium hydroxide gave an immediate precipitate of **17**, identified by spectral comparison.

Reaction of 20 with Zinc and Acetic Acid. Formation of 2,6-Lutidine. A mixture of compound **20** (1.08 g), zinc dust (2.5 g), and glacial acetic acid (25 ml) was stirred for 20 hr. Water was added, and the solution was filtered. The filtrate was extracted four times with chloroform, and the extract was washed with aqueous sodium carbonate, dried, and stripped of solvent to give 2,6-lutidine as a pale yellow oil (0.35 g, 88%), identified by infrared and ultraviolet spectral comparison with an authentic sample.

The picrate of the oil was prepared by the method of Shriner and Fuson;[42] and obtained as yellow crystals, mp 156–163°, identified as **2,6-lutidine picrate** by mixture melting point with an authentic sample, mp 156–164°.

Oxidation of 20 with Hydrogen Peroxide. Formation of 21. The procedure was adapted from that described by Baker, Querry, and Kadish[43] for the oxidation of a sulfide to a sulfone. Acetic acid (5 ml) was added to compound **20** (0.60 g) followed by aqueous 25% hydrogen peroxide (1.5 ml), and the mixture was stirred for 6 hr. The temperature was then slowly raised to 100° (external) by means of an oil bath and maintained there for 3 hr. Removal of the solvents gave a solid, which was recrystallized four times from ethanol to give **21**, mp 236–240° dec (evacuated capillary); $\lambda_{max}^{CHCl_3}$ 6.20, 6.42, 7.54, 8.78, and 9.10 μ; λ_{max}^{EtOH} 230 (ϵ 26,800) and 312 mμ (ϵ 29,500); δ^{CDCl_3} 2.52 (s, 12) and 7.52 (s, 4).

Anal. Calcd for $C_{14}H_{16}N_2O_4S$: C, 54.54; H, 5.23; N, 9.09; S, 10.35. Found: C, 54.56; H, 5.41; N, 9.12; S, 10.35.

Hydrogenation of Compound C (22). Formation of Compound D (30). Compound C (0.50 g, 1.8 mmol) was hydrogenated at atmospheric pressure in acetic acid (20 ml) in the presence of prereduced platinum oxide (50 mg). The uptake of hydrogen ceased after 3 days when *ca.* 4 molar equiv of hydrogen (186 ml, 21–25°) had been absorbed. There was no sharp break in the hydrogena-

(39) Clorox is a solution of sodium hypochlorite sold as a household bleaching agent.

(40) W. Borsche and K. Thiele, *Ber.*, **56**, 2012 (1923).

(41) A. Hantzsch, *ibid.*, **52**, 1535 (1919).

(42) Reference 33, p 180.

(43) B. R. Baker, M. V. Querry, and A. F. Kadish, *J. Org. Chem.*, **15**, 402 (1950).

tion curve. The catalyst was filtered, and the filtrate was stripped of acetic acid to give a viscous, brownish oil. Chromatography on alumina (Woelm, grade 3, neutral) in benzene and elution with benzene and ether–benzene mixtures gave compound D as a colorless oil that could not be induced to crystallize; $\lambda_{max}^{CHCl_3}$ 2.88, 2.99, 3.07, 3.16 (sh), 6.18, 6.28, 6.42, and 6.58 μ; λ_{max}^{EtOH} 275 (sh) and 303 mμ.

Compound D gave a brown color with ferric chloride in methanol, did not react with aqueous 2% potassium permanganate, could be recovered unchanged after treatment with nitrous acid, was soluble in dilute aqueous acid, but was insoluble in dilute aqueous base. It was unaffected by treatment with 5% hydrochloric acid on the steam bath for 30 min or with concentrated H_2SO_4 at room temperature for 3 hr. It did not form a picrate nor a methiodide.

Acetylation of Compound D. Formation of 31. A solution of compound D (0.38 g) in pyridine (5 ml) and acetic anhydride (3 ml) was heated on the steam bath for 1 hr and then concentrated under reduced pressure. The residual oil was chromatographed on alumina (Woelm, grade 3, neutral, 20 g) in benzene. Elution with benzene gave in the first eluates (60 ml) traces of material which was discarded. Further elution with benzene and ether–benzene mixtures containing up to 30% ether gave **31** (0.19 g, 43%) as an oil which was crystallized four times from benzene–petroleum ether with treatment with Norit to give colorless needles, mp 102.5–103°; $\lambda_{max}^{CHCl_3}$ 2.87, 3.0 (br), 5.79, 6.18, 6.29, 6.42, and 6.59 μ; λ_{max}^{EtOH} 275 (sh, ϵ 8000) and 304 mμ (ϵ 20,500).

Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.14; H, 7.49; N, 9.41.

Compound **31** gave a negative iodoform test; with aqueous ferric chloride a pinkish brown color slowly developed.

Hydrolysis of **31** was effected by treatment of a methanolic solution with aqueous 10% sodium hydroxide on the steam bath for 5 min. The reaction mixture was diluted with water and extracted with chloroform. The extract was dried and stripped of solvent to give an oil, shown to be compound D by infrared spectral comparison.

4-Amino-3-penten-2-one (23) was prepared by the general procedure of Combes and Combes.[44] Acetylacetone (9.5 g) was cooled in an ice bath, and ammonia was passed into the liquid. A white solid began to separate immediately, and after *ca.* 10 min the entire reaction mixture had solidified. This mixture was heated on the steam bath to its melting point, and treatment with ammonia was continued for an additional 10 min. The liquid was separated by distillation through a Vigreux column into three fractions; water, unconsumed acetylacetone, and product (2.5 g). The procedure was repeated with the recovered starting material, and the combined product (4.5 g, 48%) was redistilled (0.5–1 mm). Two crystallizations from ether–petroleum ether with cooling in Dry Ice–acetone gave **23** as colorless plates, mp 39–41.5° (lit.[44] mp 43°); $\lambda_{max}^{CHCl_3}$ 2.86, 3.08, 6.16, 6.26, and 6.57 μ; λ_{max}^{EtOH} 299 mμ (ϵ 16,000) [lit.[45] $\lambda_{max}^{C_6H_{12}}$ 285 mμ (ϵ 6120)]; $\delta_{max}^{CDCl_3}$ 1.88 (s, 3), 1.98 (s, 3), 5.16 (d, J = 1 Hz, 1), 6.75 (vbr), and 9.78 (v br).

4-Amino-4-(3-pyridyl-3-buten-2-one (32). Tetrahydrofuran was purified by treatment with solid potassium hydroxide under reflux for 36 hr, followed by distillation from lithium aluminum hydride. Sodium sand (1.15 g, 0.050 g-atom, prepared in xylene) was transferred to a 300-ml, three-necked flask equipped with a dropping funnel, condenser, nitrogen inlet, and magnetic stirrer; tetrahydrofuran (100 ml) was added, dry nitrogen was passed through the mixture, and the stirrer was started. Acetone (2.9 g) dissolved in tetrahydrofuran (25 ml) was added over a period of 30 min. The solution turned yellow orange and heat was evolved. Since the sodium had not reacted completely after 1 hr, more acetone (0.40 g; total, 0.057 mol) was added. After a further 30 min almost all of the sodium had reacted. A solution of 3-cyanopyridine (5.0 g, 0.048 mol) in tetrahydrofuran (25 ml) was then added over a period of *ca.* 20 min. The solution, which rapidly turned green and then brown, was heated under reflux by means of an oil bath for 2.5 hr. The cooled solution was diluted with an equal volume of water containing much ice, and immediately extracted with chloroform. The extract was dried and stripped of solvent to yield a brown oil (5.5 g) that partially solidified on being cooled at 0°. A portion of the mixture (2.5 g) was chromatographed on alumina (Woelm, grade 3, neutral, 100 g) in benzene. Unconsumed cyanopyridine (0.70 g) was eluted with benzene; elution with mixtures of ether–benzene gave small amounts of oils that were not further investigated. Elution with ether and 10% chloroform in ether afforded **32** (0.85 g, mp 84–86°. Chromatography of the remaining brown semisolid mixture yielded a further amount of **32** (total, 1.97 g, 36% based on unrecovered cyanopyridine). The product was dissolved in chloroform, treated with charcoal to remove most of the yellow color, and reprecipitated with petroleum ether; five crystallizations from benzene gave sturdy cubes, mp 92–93°; $\lambda_{max}^{CHCl_3}$ 2.84, 3.05, 6.14, 6.26, 6.40, and 6.57 μ; λ_{max}^{EtOH} 225 (ϵ 8000), 248 (ϵ 6000), and 325 mμ (ϵ 14,000); δ^{CDCl_3} 2.05 (s, 3), 5.35 (s, 1), 6.75 (br s), 7.14 (dd, J = 5 and 8 Hz), 7.75 (m), 8.43 (dd, J = 1.5 and 5 Hz), 8.63 (d, J = 1.5 Hz), and 9.50 (br s).

Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.66; H, 6.32; N, 16.89.

When a solution of **32** in 5% hydrochloric acid was warmed on the steam bath for 20 min and then made alkaline, ammonia was liberated.

Dehydration of Compound D. Formation of 37. Concentrated sulfuric acid (6 ml) was added to crude compound D (0.45 g). The resulting solution was heated on the steam bath for 2 hr, cooled, poured onto ice, and made basic with aqueous sodium hydroxide. The fine precipitate that began to form at pH 6 could not be filtered. The mixture was extracted five times with chloroform, and the extract was dried and stripped of solvent to give a pale brown oil (0.39 g) which was chromatographed on alumina (Woelm, grade 3, neutral, 10 g) in benzene. Elution with benzene and 10% ether in benzene gave **37** (0.10 g, 25%). When, in another run, Florisil (100–200 mesh) was used as adsorbent, elution with benzene and ether gave a much better yield of **37** (85%). After five recrystallizations from ether this melted at 125.5–128.5°, resolidified at 129°, and remelted sharply at 131°; $\lambda_{max}^{CHCl_3}$ 2.84, 3.06, 6.03, 6.14 (sh), 6.17, 6.28, and 10.36 μ; λ_{max}^{EtOH} 246 (ϵ 12,200) and 303 mμ (ϵ 27,000); δ^{CDCl_3} 1.90 (d, J = 6 Hz, 3), 1.98 (s, 3), 2.25 (s, 3), 2.40 (s, 3), 5.00 (s, 1), 6.65 (m, 4), and 10.00 (s, 1).

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 72.85; H, 8.08; N, 11.91.

Compound **37** reacted with bromine in carbon tetrachloride without the liberation of hydrogen bromide, forming a yellow precipitate.

Hydrogenation of 37. Formation of 38. Compound **37** (21.8 mg, 0.095 mmol) was hydrogenated in ethanol (2 ml) over palladium–charcoal at atmospheric pressure. After 20 min no further hydrogen was consumed; the total uptake of hydrogen was 0.91 molar equiv (2.24 ml, 24°). The catalyst was removed by centrifugation, and the solvent was evaporated to give **38** as an oil (21 mg) that solidified on being scratched. Crystallization from ethanol–water followed by sublimation (100°, 0.3 mm) gave colorless needles; these melted at 113–115°, resolidified, and remelted sharply at 130°; $\lambda_{max}^{CHCl_3}$ 2.84, 3.05, 6.16, 6.28, 6.40, and 6.55 (br) μ; λ_{max}^{EtOH} 275 (sh) (ϵ 8400) and 303 mμ (ϵ 20,000); δ^{CDCl_3} 0.93 (t, J = 6 Hz, 3), 1.95 (s, 3) superimposed on 1.5 (m, 2), 2.28 (s, 3), 2.45 (s, 3) superimposed on 2.5 (m, 3), 4.88 (s, 1), 6.18 (br d, 1), 6.68 (s, 1), and 9.28 (br d, 1).

Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.56; H, 8.65; N, 12.25.

Determination of the Basicities of 37, 38, and Some Substituted Pyridines.[46] A mixture of 50% (v/v) ethanol–water, prepared in one batch, was used in all the dilutions. Sodium hydroxide and hydrochloric acid solutions were prepared in 50% ethanol–water. Two ml of 0.0583 *M* aqueous potassium acid phthalate solution was diluted with 25 ml of the 50% ethanol–water mixture and titrated potentiometrically (Beckman pH meter, glass electrode against standard calomel electrode) with the sodium hydroxide solution, which was found to be 0.0789 *N*. The hydrochloric acid solution, standardized against the sodium hydroxide solution, was 0.0902 *N*.

The compound (20 mg) was dissolved in 50% ethanol–water (25 ml), excess hydrochloric acid (3.5 ml) was added, the solution was stirred magnetically, and the pyridine salt was titrated with sodium hydroxide. The pH was measured as above, and the half-point acidities were obtained graphically; measurements were made at increments of 0.10 ml initially, and of 0.01 ml when the slope of the plot of pH *vs.* added base changed. The pK_a's of the conjugate acids of the bases, taken as the half-point pH's, are given in Table IV.

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Treatment of 3 with Polyphosphoric Acid. Formation of 5, 22, and Compound E (46). A mixture of polyphosphoric acid (44 g) and dioxime **3** (2.50 g) was stirred in an oil bath (preheated to 120°) until its temperature reached 110° and was then maintained at this temperature for 15 min. It was poured onto ice, and the resulting brown solution was extracted continuously with chloroform for 50 hr. Removal of the chloroform gave an oil (2.5 g) which was chromatographed on alumina (Woelm, grade 3, neutral, 100 g) in benzene. Elution with benzene gave in the early fractions compound E (0.05 g, 2%); later benzene fractions afforded compound **5** (1.17 g, 47%). Mixtures of ether and benzene eluted compound **22** (0.84 g, 34%), and 5% chloroform in ether eluted a substance (0.20 g) that after recrystallization from chloroform–ether had mp 216–219°. In a second run, none of the last compound could be isolated, but ether and 5% chloroform eluted another substance, mp 208–209°, in low yield.

Compound E was triturated with ether and recrystallized three times from ether–petroleum ether and once from ether with cooling in a Dry Ice–acetone bath to give colorless crystals, mp 109.5–110.5°; $\lambda_{max}^{CHCl_3}$ 6.10, 6.24, and 6.37 μ; λ_{max}^{EtOH} 210 (ϵ 42,000), 318 mμ (ϵ 6100), and several peaks at 260–290 mμ (see Figure 1); δ^{CDCl_3} 2.08 (s, 3), 2.30 (s, 3), 2.48 (s, 3), 2.83 (s, 3), 5.98 (s, 1), and 7.10 (s, 1),

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56; mol wt, 242. Found: C, 69.03; H, 5.99; N, 11.07; mol wt [Rast (exaltone)], 255.

3-Methylanthranil (45) was prepared by the method of Bamberger and Elger[47] by reduction of *o*-nitroacetophenone with tin foil and acetic acid; fractional distillation gave a middle fraction, bp 75–77° (1.5 mm) [lit.[47] bp 110.5–111° (10 mm)]; $\lambda_{max}^{CHCl_3}$ 6.08, 6.20, 6.33, and 6.39 μ; λ_{max}^{EtOH} end absorption (ϵ_{210} 12,000), 316 mμ (ϵ 5800) and several peaks at 245–280 mμ (see Figure 1); δ^{CDCl_3} 2.73 (s, 3) and 7.25 (m, 4).

Dioxime of the Photodimer of 2,6-Diethyl-4-pyrone (4). The photodimer of 2,6-diethyl-4-pyrone (**2**)[5] was converted to its dioxime by the procedure used for the preparation of the dioxime of the photodimer of 2,6-dimethyl-4-pyrone (*vide supra*). After three recrystallizations from large amounts of acetonitrile it had mp 263–267° dec; λ_{max}^{Nujol} 3.05 and 6.05 μ; λ_{max}^{EtOH} 232 mμ (ϵ 16,900),

Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.61; H, 7,78; N, 8.42.

Treatment of 4 with Sulfuric Acid. Formation of 49 and 50 and Compounds F and G. The dioxime **4** (6.00 g) was treated with concentrated sulfuric acid under the same conditions as used for the dioxime **3**. The resulting brown oil was chromatographed on alumina (Woelm, grade 3, neutral, 180 g) in benzene. Benzene eluted the liquid **49** (1.18 g, 20%); elution with mixtures of 2% and 5% ether in benzene gave oils (1.15 g) that contained **49** and other substances that were not isolated; 25% ether in benzene eluted compound F (0.20 g, 3%); elution with 25% and 50% ether in benzene gave mixtures of compounds F and G (0.88 g, 15%); ether and 2% chloroform in ether eluted **50** (0.35 g, 6%).

Compound **49** was purified by two molecular distillations (120°, 0.3 mm), when it was obtained as a colorless liquid; λ_{max}^{neat} 5.81 and 6.24 μ; λ_{max}^{EtOH} 217 mμ (ϵ 6600).

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.82; H, 7.67; N, 8.35.

The 2,4-dinitrophenylhydrazone of 49 was prepared by the method of Shriner and Fuson[33] and chromatographed on alumina (Woelm, grade 3, neutral). It was crystallized three times from ethanol to give fine yellow needles, mp 91–91.5°; λ_{max}^{EtOH} 220 (ϵ 13,600), 267 (ϵ 7000), and 356 mμ (ϵ 22,900).

Anal. Calcd for $C_{15}H_{17}N_5O_5$: C, 51.87; H, 4,93; N, 20.17. Found: C, 51.92; H, 5.07; N, 20.11.

Compound **50** was freed from small amounts of compound G by sublimation. The sublimate was recrystallized five times from ether with cooling in a Dry Ice–acetone bath to give colorless crystals, mp 69.5–70.5°; $\lambda_{max}^{CHCl_3}$ 2.75, 3.05 (br), 5.93, and 6.17 μ; λ_{max}^{EtOH} 265 mμ (ϵ 12,500).

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8,38. Found: C, 64.17; H, 7.97; N, 8.16.

Treatment of **50** with acetic anhydride and pyridine on the steam bath for 1 hr gave an acetate; $\lambda_{max}^{CHCl_3}$ 5.70, 5.94, 6.23, and 6.36 μ.

Compound G was obtained by rinsing the residue from the above sublimation with benzene followed by two crystallizations from the same solvent, mp 212° dec; λ_{max}^{EtOH} 265 mμ (ϵ 27,300).

Anal. Calcd for $C_{18}H_{26}N_2O_4 \cdot 0.5C_6H_6$: C, 67,53; H, 7.83; N, 7,50. Found: C, 67.45; H, 7.80; N, 7.47.

The benzene of solvation could be removed by heating at 100° (0.02 mm) for 24 hr; λ_{max}^{Nujol} 3–4 and 6.10 μ; λ_{max}^{EtOH} 264 mμ (ϵ 33,600).

Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64,65; H, 7,84; N, 8.38. Found: C, 64,52; H, 7,69; N, 8.37.

The mixture of compounds F and G from the original chromatogram was subjected to sublimation to remove **50**, present as a contaminant, and was then rechromatographed on alumina (Woelm, grade 3, neutral, 50 g) in 20% ether in benzene. Elution with 50% ether–benzene gave **compound F** which was crystallized from benzene and then combined with compound F from the original chromatogram and recrystallized three times from benzene; mp 192.5–193°; $\lambda_{max}^{CHCl_3}$ 3–4, 6.05, and 6,14 μ (sh); λ_{max}^{EtOH} 263 mμ (ϵ 34,000),

Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8,38, Found: C, 64.79; H, 7.75; N, 8.22,

Dioxime of the *seco* Dimer of 2,6-Dimethyl-4-pyrone (54). A mixture of the *seco* dimer **55**,[4] hydroxylamine hydrochloride, and pyridine was heated on the steam bath for 10 min and then allowed to stand overnight. Removal of pyridine and addition of water gave **54** as a colorless crystalline solid, mp 180–190° dec. After two recrystallizations from pyridine–water and one from ethanol–water, it had mp 218–220° dec; λ_{max}^{Nujol} 3–4, 6,02 (sh), and 6.08 μ; λ_{max}^{EtOH} 262 mμ (ϵ 29,200).

Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10,07, Found: C, 60.13; H, 6.64; N, 9.81.

Acetylation of 4. Formation of 58 and 59. A mixture of dioxime **4** (2.50 g), acetic anhydride (8 ml), and pyridine (20 ml) was heated on the steam bath. After 4 hr not all of the dioxime had dissolved, more pyridine (10 ml) was added, and the solution was heated for an additional 3 hr. It was then concentrated under reduced pressure to *ca.* 15 ml and cooled. The crystals that separated were filtered and rinsed with ether to give **58** (1.70 g, 68%). After four recrystallizations from chloroform–benzene, it had mp 219–222° dec (evacuated capillary); $\lambda_{max}^{CHCl_3}$ 5.67, 6.10, 10.90, and 11,75 μ; δ^{CDCl_3} 0.90 (t, J = 7 Hz, 12), 1.76 (q, J = 7 Hz, 8), 2.18 (s, 6), 3.32 (br s, 2), and 3.90 (br s, 2).

Anal. Calcd for $C_{22}H_{30}N_2O_6$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.21; H, 7.27; N, 6.45.

Water was added to the original filtrate and the precipitate (0.80 g) was crystallized from benzene. The first crop of crystals consisted mainly of **58**, subsequent crops after recrystallization and sublimation gave **59** (0.35 g, 14%), mp 170–171°; $\lambda_{max}^{CHCl_3}$ 5.67, 6.10, 10.75, and 11.58 μ; nmr spectrum indistinguishable from that of **58**.

Anal. Calcd for $C_{22}H_{30}N_2O_6$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63,21; H, 7.30; N, 6.48.

The acetates were hydrolyzed by brief warming of an ethanolic solution with a few drops of aqueous 10% sodium hydroxide. The crude product from the diacetate, mp 170–171°, began to decompose at 265° and melted at 278°; the product from the diacetate, mp 219–222°, melted at 284° with gas evolution. The infrared spectra of the products differed only to a minor extent; the former had λ_{max}^{Nujol} 6.06, 8.61, 9.55, 10.05 (sh), 10.17 (sh), 10.31, and 10.59 μ, and the latter had λ_{max}^{Nujol} 6.07, 8.61, 9.55 (the latter two bands were relatively less intense than in the spectrum of the other compound), 10.21 (sh), and 10.37 μ.

Acetylation of 3. A mixture of dioxime **3** (0.90 g), acetic anhydride (10 ml), and pyridine (25 ml) was heated on the steam bath for 14 hr. The solution was cooled, and the precipitate (0.86 g, 74%) was filtered and crystallized three times from large amounts of chloroform. It did not melt, but began to turn brown at 275° and had turned black at 300°; $\lambda_{max}^{CHCl_3}$ 5.68 and 6.11 μ.

Anal. Calcd for $C_{18}H_{22}N_2O_6$: C, 59.66; H, 6.12; N, 7.73. Found: C, 58.90; H, 6.34; N, 7.87.

Further crops obtained from the mother liquors all had infrared spectra superimposable on the spectrum of the recrystallized solid.

Treatment of 4 with Polyphosphoric Acid. When the dioxime **4** was treated with polyphosphoric acid under the same conditions as in the case of the dioxime **3**, a brown liquid was obtained which on chromatography yielded the same products as those obtained in the sulfuric acid treatment of **4**.

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