2β-Chloro-3-tropinones 5 and 2β-Chloropseudopelletierine (13). 2-Chloro-2,6-cycloheptadienone (4) (R = R′ = H) (0.510 g, 3.60 mmol) was dissolved in methanol (20 mL) and cooled to 0 °C. Aqueous methylamine (1.40 mL of a 12.9 M aqueous solution, 18.1 mmol) was introduced via syringe and the temperature maintained for 1.0 h, then the reaction mixture was partitioned between methylene chloride and water. The aqueous phase was reextracted with methylene chloride, then the combined organics were dried over calcium chloride and the solvent removed in vacuo. Chromatography [Florisil, ether (75%)–petroleum ether (25%)] afforded 2β-chloro-3-tropinone (5) (R = R′ = H) as a light oil (which solidifies at 0 °C) (0.386 g, 62%): ^{1}H NMR ($CDCl_3$) δ 1.65–2.05 (7, 4 H), 2.42 (d, d, J = 15.5 and 2.0 Hz, 1 H), 2.59 (s, 3 H), 2.80 (d, d, J = 15.5 and 4.0 Hz, 1 H), 3.60 (m, 2 H), 4.70 (d, J = 4.0 Hz, 1 H); IR (neat) ν_{max} = 1725, 1140 cm^{-1}; MS m/e (rel intensity) 173 (24.3), 110 (39), 96 (48), 82 (100).

Utilizing identical experiment procedures, 2-chlorocycloheptadienone (4) (R = Me; R′ = H) (0.589 g, 3.45 mmol) was transformed into 2β-chloro-5-methyltropinone (5) (R = Me; R′ = H) (0.424 g, 2.28 mmol, 66%); 2-chlorocycloheptadienone (4) (R = Me; R′ = isopropenyl) (0.770 g, 3.94 mmol) was converted into the tropinone analogue 5 (R = Me; R′ = isopropenyl) (0.442 g, 1.93 mmol, 49%); and bicyclic alcohol 11 (0.834 g, 4.37 mmol) was converted into 2β-chloropseudopelletierine (13) (0.379 g, 2.01 mmol, 46%).

3-Tropinones 6, 7, and 8 and Pseudopelletierine (14). 2β-Chloro-3-tropinone (5) (R = R′ = H) (0.386 g, 2.23 mmol) was dissolved in benzene (10 mL) to which tri-n-butyltin hydride (2.00 g, 7.0 mmol) and azoisobutyronitrile (~30 mg) were added. The solution was refluxed until consumption of starting material was complete (~1 h), then the reaction was cooled and partitioned between 10% aqueous hydrochloric acid and ether. The pH of the aqueous layer was adjusted to 10 and the aqueous layer extracted with methylene chloride twice. The organics were dried over calcium chloride, and the solvent was removed in vacuo. Filtration of the residue through Florisil gave (±)-tropinone (6) (R = R′ = H) (0.158 g, 70%) identical in spectral and physical characteristics with an authentic sample.

With the use of an identical experimental procedure, chlorotropinone (5) (R = Me; R′ = H) (0.586 g, 3.45 mmol) was dechlorinated to yield tropinone analogue 7 (0.284 g, 1.79 mmol, 52%); chlorotropinone (5) (R = Me; R′ = isopropenyl) (0.442 g, 1.93 mmol) was reduced to isomeric tropinone analogues 8 (0.215 g, 1.09 mmol, 56%); and chloropseudopelletierine 13 (0.379 g, 2.01 mmol) was transformed into pseudopelletierine (0.284g, 0.190 mmol, 94%), identical in physical and spectral characteristics with an authentic sample.

Acknowledgment. We are grateful for support of these studies by the University Research Council of Vanderbilt University.

Rearrangement-Hydrolysis of 5-Amino-1,2,4-Benzothiadiazines[1]

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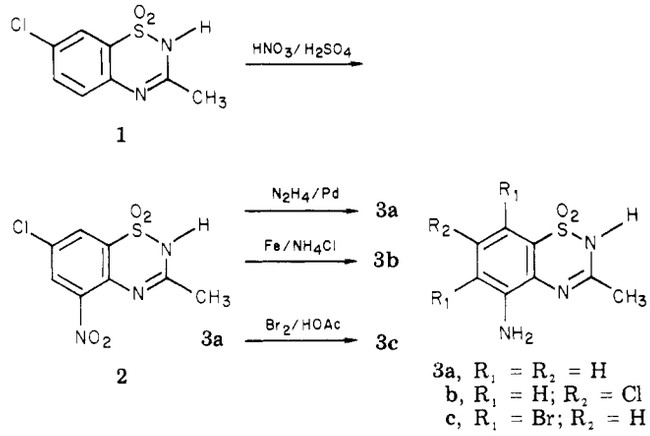
Several compounds are known which exert a biological action on the pancreas and thus have been chosen for study as diagnostic radioactive pancreatic imaging agents.[2] 7-Chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (1) and closely related analogues are known hyperglycemics which appear to have a direct pancreatic effect.[3] Studies in our laboratory directed to the preparation of radioiodinated 1,2,4-benzothiadiazines for study in hamsters bearing pancreatic tumors[4] have uncovered a unique rearrangement–hydrolysis induced by diazotization of 5-amino-1,2,4-benzothiadiazine 1,1-dioxides.

Nitration of 1 in warm nitric/sulfuric acid gave 5-nitro-7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (2) in 64% yield. Reduction of the nitro group by



hydrazine, palladium, and ethanol effected a simultaneous dehalogenation to 5-amino-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (**3a**). Iron–ammonium chloride reduction of **2** gave the chloro-containing amine (**3b**), while direct bromination of **3a** gave the 6,8-dibromo analogue (**3c**) in 57% yield.

Diazotization and iodination of **3a–c** by standard Sandmeyer methods gave products lacking iodine but possessing, by elemental analysis and mass spectral measurement, the elements of the diazo function and 1 equiv of water. The methyl ^{1}H NMR signals of the diazotized products revealed an upfield shift of approximately 0.4 ppm in each case. Furthermore, the ready solubility of the products in dilute base and the typical primary sulfonamide N–H bands[5] at 3085–3350 cm^{-1} implicated the presence of the SO_2NH_2 group. A sharp carbonyl absorption was also evident in these diazotized products at 1718–1728 cm^{-1} and taken with the 43 amu base peak in their mass spectra pointed to the presence of an acetyl function. The 1-acetylbenzotriazoles (**5a–c**) represent structural entities in accord with the available spectral and physical data.

The reported C=O stretch for similar 1-acetylbenzotriazoles is a uniquely similar high wavenumber absorption to that detected in the diazotized derivatives of **3a–c**.[6] In addition, support for the assignment of structures **5a–c** to the product can be found in the successive mass spectral fragmentation of 42 and 28 amu from the parent ions. Sequential loss of a ketene equivalent and nitrogen characterize the published cracking patterns of other 1-acetylbenzotriazoles.[7]

A logical pathway for the reaction would be interception of the intermediate diazonium function by N-4 of the

(1) (a) Supported in part by Grant No. CA 14043 from the National Cancer Institute. (b) Abstracted from the Ph.D. Thesis of E. G. C., Lehigh University, 1979. (c) The assistance of the Kresge Foundation in the purchase of the mass spectrometer used in these studies is acknowledged with appreciation.

(2) V. R. Risch in "The Chemistry of Radiopharmaceuticals", N. D. Heindel, H. D. Burns, and T. Honda, Eds., Masson USA, New York, 1978, Chapter 4.

(3) A. Loubatieres, M. Mariani, and R. Alric, *Ann. N.Y. Acad. Sci.*, **150**, 226 (1968).

(4) For a typical study of this type on other candidate agents see: V. R. Risch, T. Honda, N. D. Heindel, J. L. Emrich, and L. W. Brady, *Radiology*, **124**, 837 (1978).

(5) Sadtler Standard Grating Spectra No. 10670K and 15929K, 1968.

(6) D. G. O'Sullivan, *J. Chem. Soc.*, 3853 (1960).

(7) M. Ohashi, K. Tsujimoto, A. Yoshino, and T. Yonezawa, *Org. Mass Spectrosc.*, **4**, 203 (1970).

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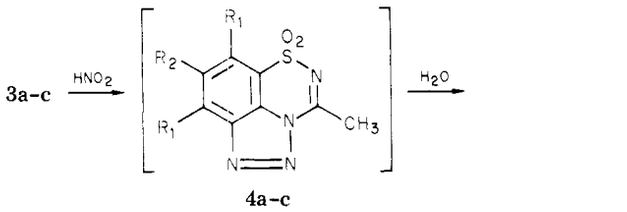
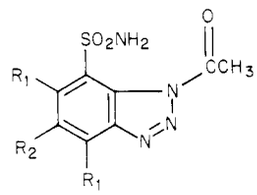
benzothiadiazine ring to yield a bridged tricyclic triazolo transient (4), which undergoes facile hydrolysis to **5a–c**.

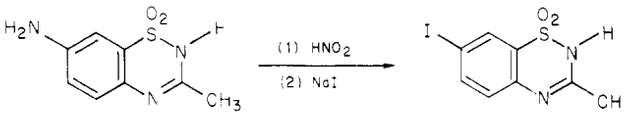


4a–c



5a–c

Reactions involving triazolo bridging of amines peri to ring heterocyclic nitrogens have been reported in 8-amino-4-(1*H*)-quinolinones[8] and 5-aminobenzomorpholines.[9] Strain and electronic activation by the triazolo ring on the incipient carbonyl carbon in **4a–c** are necessary criteria for hydrolysis to take place; the noncyclic diazonium ion intermediate does not appear to sufficiently labilize the ring carbon for attack by water. Diazotization of 7-amino-3-methyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**6**) followed by treatment with NaI yielded the corresponding 7-iodo derivative (**7**) without evidence of the hydrolytic scission of the thiadiazine ring.



6 **7**

Experimental Section

Melting points are uncorrected and were obtained on a Thomas-Hoover apparatus. Infrared spectra were run as Nujol mulls on a Perkin-Elmer 283 spectrophotometer. Proton NMR were obtained with a Hitachi Perkin-Elmer R20A, and mass spectra were run on a Finnigan Model 4021 automated GC–MS system. Elemental analyses were performed by Dr. George Robertson, Florham Park, N.J.

7-Chloro-5-nitro-3-methyl-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (2). To a solution of 20 mL of concentrated HNO_3 and 50 mL of concentrated H_2SO_4 being maintained at 70 °C was added 4.00 g (17.0 mmol) of 7-chloro-3-methyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide.[10] The solution was held at 70 °C for 2 h with continuous agitation and was then poured carefully into approximately 400 mL of ice–water. The precipitate was collected, dried, and recrystallized from ethyl acetate to return 3.00 g (64%) of **2**: mp 276–279 °C (lit.[11] 273–275 °C).

Anal. Calcd for $C_8H_6ClN_3O_4S$: C, 34.85; H, 2.19; N, 15.24. Found: C, 34.77; H, 2.24; N, 15.38.

5-Amino-3-methyl-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (3a). A 0.67-g (2.43 mmol) portion of **2** was dissolved in 100 mL of 95% ethanol, heated to 50 °C, and treated to the cautious addition of 0.10 g of 10% palladium on charcoal slurried in 15 mL of 95% ethanol. To this suspension was added 14 mL of hydrazine hydrate in a dropwise fashion over 15 min followed by the readdition of 0.10 g of the palladium catalyst in 15 mL of ethanol. The reaction mixture was stirred at reflux for 2 h, filtered while hot through a pad of Celite, and concentrated in vacuo to half-volume. After addition of 100 mL of water the pH was adjusted to neutrality with 6 N aqueous HCl and again concentrated in vacuo until crystals began to precipitate. Chilling of the medium in ice, filtration of the product, and recrystallization from MeOH with addition of water to induce turbidity gave 0.42 g (82%) of colorless needles of **3a**: mp 229–231 °C; IR 3435, 3333, 3285 cm^{-1} (N–H); ^1H NMR (Me_2SO-d_6) δ 2.35 (s, 3 H, CH_3), 6.80–7.20 (m, 3 H, Ar**H**). Anal. Calcd for $C_8H_9N_3O_2S$: C, 45.48; H, 4.29; N, 19.89. Found: C, 45.55; H, 4.38; N, 20.20.

7-Chloro-5-amino-3-methyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (3b). A suspension was prepared from 2.00 g (7.25 mmol) of **2**, 100 mL of 70% MeOH–30% water, and 2.50 g of ammonium chloride was heated to reflux with stirring and treated to the portionwise addition of 2.50 g of activated iron powder over a 30-min period. Reflux and stirring were continued for 8 h, the mixture was filtered while hot through Celite, and the filter cake was washed throughly with 150 mL of hot MeOH. The filtrate and washings were added to 275 mL of water, refluxed for 5 min, and refiltered while hot through Celite. Chilling to 0 °C caused the precipitation of 1.60 g of a crude crystal crop which was recrystallized twice from EtOH (by addition of water to turbidity) with the aid of decolorizing carbon to give 0.90 g (51%) of **3b**: mp 316–318 °C dec; IR 3432, 3377, 3287 cm^{-1} (NH); ^1H NMR (Me_2SO-d_6) 2.34 (s, 3 H, CH_3), 6.96 (m, 2 H, Ar**H**).

Anal. Calcd for $C_8H_8ClN_3O_2S$: C, 39.11; H, 3.28; N, 17.10. Found: C, 39.01; H, 3.35; N, 17.03.

5-Amino-6,8-dibromo-3-methyl-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (3c). To 40 mL of glacial acetic acid containing 0.40 g (1.89 mmol) of **3a** was added, dropwise, 0.60 g (3.75 mmol) of bromine. The solution was heated to 60 °C for 2 h, chilled, and filtered to yield 0.52 g of crude product. The material was recrystallized from MeOH–water to which had been added a small quantity of $NaHCO_3$ and gave 0.40 g (53%) of **3c** as a hydrate: mp 281–282 °C; IR 3350, 3247 cm^{-1} (NH); ^1H NMR (Me_2SO-d_6) δ 2.33 (s, 3 H, CH_3), 7.70 (s, 1 H, Ar**H**).

Anal. Calcd for $C_8H_7Br_2N_3O_2S{\cdot}H_2O$: C, 24.82; H, 2.34; N, 10.85. Found: C, 24.75; H, 2.39; N, 10.88.

1-Acetyl-7-sulfonamido-1*H*-benzotriazoles (5a–c). A solution prepared from 30 mL of water, 5 mL of concentrated aqueous HCl, and 1.0 mmol of **3a** or **3b** was chilled to ice–water bath temperature. The diminished solubility of **3c**, 1.0 mmol, required its preparation as a partly dissolved suspension in 25 mL of water, 5 mL of concentrated aqueous HCl, 25 mL of glacial acetic acid, and 25 mL of ethanol. To each of these reaction media 1.10 mmol of sodium nitrite in 1 mL of water was added and the contents of the reaction vessels were stirred vigorously at ice bath temperatures (0–5 °C) for 2.5 h and then at room temperature for 2 h. Filtration gave the title compounds (**5a–c**) which were recrystallized from ethanol and water to analytical purity. Compound **5a** was obtained in 76% yield: mp 263–264 °C; IR 3276, 3090 (NH), 1718 cm^{-1} (C=O); ^1H NMR (Me_2SO-d_6) 1.99 (s, 3 H, CH_3), 7.57–8.45 (m, 3 H, Ar**H**); mass spectrum 240 (M^+), 198, 170, 43 amu (base peak).

Anal. Calcd for $C_8H_8N_4O_3S$: C, 39.99; H, 3.36; N, 23.32. Found: C, 39.51; H, 3.33; N, 23.39.

Compound **5b** was obtained in 85% yield: mp 261–263 °C; IR 3312, 3092 (NH), 1728 cm^{-1} (C=O); ^1H NMR (Me_2SO-d_6) δ 1.98 (s, 3 H, CH_3), 7.95 (d, 1 H, Ar**H**, J = 3 Hz), 8.52 (d, 1 H, ArH, J = 3 Hz); mass spectrum 274 (M^+), 232, 204, 43 amu (base peak).

Anal. Calcd for $C_8H_7ClN_4O_3S$: C, 34.98; H, 2.57; N, 20.39. Found: C, 34.75; H, 2.73; N, 20.24.

Compound **5c** was obtained in 50% yield: mp 296–298 °C; IR 3295, 3085 (NH), 1723 cm^{-1} (C=O); ^1H NMR (Me_2SO-d_6) δ 1.99 (s, 3 H, CH_3), 8.20 (s, 1 H, Ar**H**); mass spectrum 396 (M^+), 354, 326, 43 amu (base peak).

Anal. Calcd for $C_8H_6Br_2N_4O_3S$: C, 24.14; H, 1.52; N, 14.08. Found: C, 24.41; H, 1.63; N, 13.93.

7-Iodo-3-methyl-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (7). To a solution of 0.5 mmol of 7-amino-3-methyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide[12] (**6**) in 1.5 mL of concentrated HCl and 10 mL of water at 0 °C was added 0.58 mmol of $NaNO_2$ in 1 mL

(8) B. E. Halcrow and W. O. Kermack, *J. Chem. Soc.*, 415 (1945).
(9) J. R. Jurgens, A. L. Burton, A. Eichenbaum, and L. B. Clapp, Jr., *J. Org. Chem.*, **25**, 1710 (1960).
(10) We acknowledge with appreciation the generous gift of this material from the Schering Corp.
(11) A. Monzani, M. DiBella, U. Fabio, and G. Manicardi, *Farm. Ed. Sci.*, **28** 149 (1973).
(12) J. G. Topliss, M. H. Sherlock, H. Reimann, L. M. Konzelman, E. P. Shapiro, B. W. Pettersen, H. Schneider, and N. Sperber, *J. Med. Chem.*, 6, 122 (1963).

of water. The solution was stirred in an ice bath for 30 min. Then 0.625 mmol of NaI in 2.5 mL of water was added. The mixture was stirred in an ice bath for 2 h and warmed to 40 °C for 90 min. Sodium bisulfite was added to reduce any iodine. The product was filtered and recrystallized from methanol/water to yield 90 mg (56%) of **7**: mp 325–328 °C (lit.[13] 330–331 °C).

Registry No. 1, 364-98-7; **2**, 37157-79-2; **3a**, 71870-66-1; **3b**, 71870-67-2; **3c**, 71870-68-3; **5a**, 71870-69-4; **5b**, 71870-70-7; **5c**, 71870-71-8; **6**, 71870-72-9; **7**, 37148-02-0.

(13) J. G. Topliss and M. D. Yudis, *J. Med. Chem.*, **15**, 400 (1972).

Some Reactions of Enamine Adducts of 3,4-Diazacyclopentadienone 3,4-Dioxides

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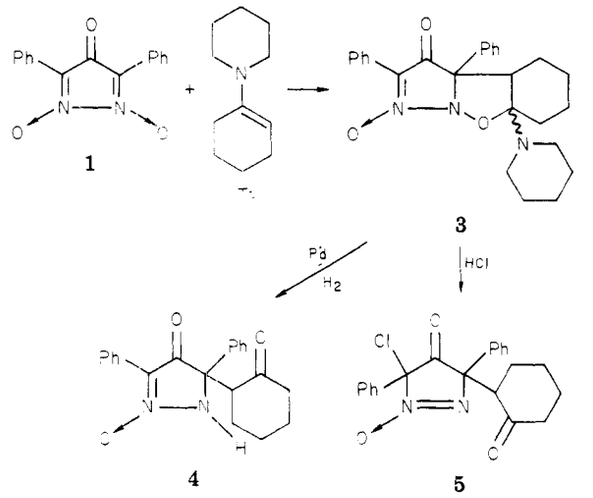
The formation of cycloadducts from diazacyclopentadienone dioxides and alkenes, and some of the reactions of these cycloadducts, have been reported.[1] Since the regiospecificity of enamine cycloadditions to the nitrone function[2] provides a masked carbonyl function, we have examined briefly the formation, hydrolysis, and hydrogenolysis of these cycloadducts in this novel system.

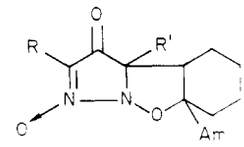
The diazacyclopentadienone dioxides react rapidly and almost quantitatively with enamines under mild conditions to yield the desired cycloadducts[3] (Table I). Cycloadduct **3**, formed from 2,5-diphenyl-3,4-diazacyclopentadienone



3,4-dioxide (**1**) and *N*-cyclohexenylpiperidine (**2**), was reduced rapidly at room temperature by hydrogen on palladium to yield the pyrazolone *N*-oxide **4** in good yield. This same compound was also obtained upon treatment of **3** with sodium dithionite, but this reaction was less clean.

The structure of **4** rests upon its spectral properties (see Experimental section), the similarity of its mass spectral

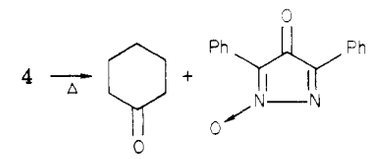
Table I. Enamine Cycloadducts



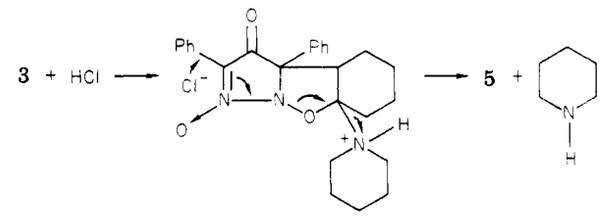
compd			mp, °C[a,b]	yield, %
R	R'	Am		
C_6H_5	C_6H_5	morpholine	113–115	96
C_6H_5	CH_3	morpholine	63–65	70
C_6H_5	C_6H_5	pyrrolidine	136–138	93
C_6H_5	CH_3CH_2	pyrrolidine	128–130	97
C_6H_5	CH_3	pyrrolidine	118–120	92
C_6H_5	C_6H_5	piperidine	143–145	93

[a] After recrystallization from CH_2Cl_2-petroleum ether. [b] Satisfactory analytical data (±0.3 for C, H, N) were obtained and reported for all compounds except for the first entry which tenaciously retained solvent.

cracking pattern to that of other 4-ketopyrazoline 2-oxides,[1,4] and its decomposition at its melting point to produce cyclohexanone and 2,5-diphenyl-3,4-diazacyclopentadienone 3-oxide.[5,6]



Treatment of **3** with hydrochloric acid in methanol at room temperature produced the halogenated pyrazolone *N*-oxide **5**. This compound may arise as follows:[7]



In the absence of a nucleophilic anion, **3** was stable to acid treatment. Thus similar treatment with aqueous perchloric acid produced no cleavage; harsher conditions were not examined, however.

The structure of **5** rests upon its elemental analysis and its spectral properties (M^+ in mass spectrum, $\gamma_{N=NO}$ 1570 cm^{-1} in its infrared spectrum). The proposed mechanism is consistent with the known reactivity of the nitrone carbon toward nucleophiles (cf. the rearrangement of the acetylene adducts of **1**[1]) and with other nucleophilic additions, even to aromatic rings, which accompany heterolytic cleavage of N–O bonds.[8]

The importance of the nucleophilic addition to the cleavage of the oxazolidine ring was also shown by the stability of the cycloadducts **6** and **7** (obtained in two diastereomeric forms) to acid hydrolysis; neither reacted

(1) J. P. Freeman and M. J. Hoare, *J. Org. Chem.*, **36**, 19 (1971).
(2) (a) D. St. C. Black, R. F. Crozier, and V. C. Davis, *Synthesis*, 205 (1975); (b) Y. Takeuchi and F. Furusaki, "Advances in Heterocyclic Chemistry", Vol. 21, A. R. Katritzky and A. J. Boulton, Eds., Academic Press, New York, 1977, p 201.
(3) As with other dipolarophiles, cycloaddition of unsymmetrical derivatives of **1** always occurred at the alkyl-substituted nitrone function,[1] as revealed by the upfield shift of the alkyl group hydrogens in their NMR spectra.
(4) J. P. Freeman, *J. Org. Chem.*, **27**, 2881 (1962).
(5) J. P. Freeman, J. J. Gannon, and D. L. Surbey, *J. Org. Chem.*, **34**, 187 (1969).
(6) In other work we have observed that adducts of **6** and stable enolates, e.g., that from ethyl benzoylacetate, form but readily reverse to starting materials upon heating.
(7) The reaction need not be concerted but could involve prior addition of HCl to the nitrone function followed by elimination to form the N=N bond.
(8) Inter Alia: R. Fielden, O. Meth-Cohn, and H. Suschitsky, *J. Chem. Soc., Perkin Trans. 1*, 705 (1973); A. Picot and X. Lisinchi, *Tetrahedron Lett.*, 903 (1973); P. G. Gassman, G. A. Campbell, and G. Mehta, *Tetrahedron*, **28**, 2749 (1972).

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