Directive Influence of the Keto Bridge on the Isomerization Pathways of 2,3-Dicarbonyl-2,3-diazanorbornen-7-one Derivatives

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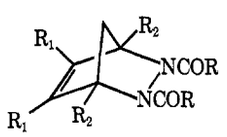
Received August 17, 1972

The keto bridge in the adducts **5** of 2,5-dimethyl-3,4-diphenylcyclopentadienone with azo esters profoundly increases the lability of the adducts toward clean thermal isomerization. A reversible [3,3] sigmatropic rearrangement to the 1,3,4-oxadiazine derivatives **6** is observed, along with a slower, and perhaps irreversible, [1,3] sigmatropic rearrangement to the diazetidines **7**, the stable thermal end products. Both the isomerizations of **5** to **6** and **5** to **7** can be reversed by photolysis, which also causes decarbonylation of **5** to the 1,2-dihydropyridazine esters **10**. Reaction of the cyclone with azodiacyls leads to the quantitative isolation of the oxadiazines **16**, but the intermediacy of the initial Diels–Alder adduct **15** could be shown by nmr spectroscopy.

We have recently shown[1,2] that the adducts **1** from azodiacyls and cyclopentadiene undergo a [3,3] sigmatropic rearrangement to the racemic oxadiazines **2**



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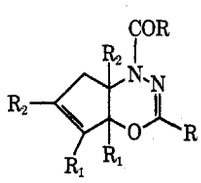

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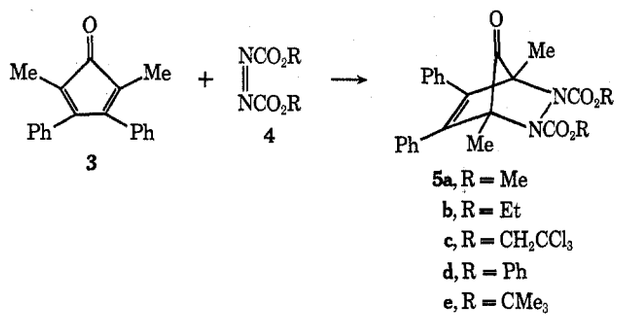


3 **4** **5a**, R = Me; **b**, R = Et; **c**, R = CH_2CCl_3; **d**, R = Ph; **e**, R = CMe_3

(one enantiomer from each of two pathways) under circumstances which indicated that the reaction was concerted. Accelerating effects were noted by increasing the bulk of R in the amide group,[2] and by the presence of vinyl (R_1) and bridgehead (R_2) substituents.[1] Replacement of the amide by urethane groups (R = acyloxy), however, completely inhibited the rearrangement.[3]

We now wish to report that a keto bridge lowers remarkably the thermal stability of the diazanorbornene system in the adducts of both azodiacyls and azo esters, and that, in particular, in the case of the adducts **5** of azo esters with 2,5-dimethyl-3,4-diphenylcyclopentadienone a delicately balanced set of competing isomerizations is observed.

Results

The reaction of the cyclone **3** (as its dimer) with the azo esters **4** was conveniently followed in refluxing carbon tetrachloride by nmr spectroscopy, which showed the buld-up of the *tert*-methyl singlet in the adducts **5**. In the late stages additional methyl singlets began to appear before reaction of **3** and **4** was complete. The optimum reflux times for each azo ester (yields of at least 90%) are shown in Table I and point out their wide variation in reactivity. The adducts **5a** and **5d** were crystalline and the others were glassy solids; spectroscopic properties of interest are also listed in Table I.

The peaks developing in the nmr spectrum during the late stages of the azo ester reactions were again observed when solutions of the pure adducts **5** were refluxed, slowly in carbon tetrachloride, more rapidly in tetrachloroethylene. Specifically, a solution of **5a** showed eight new methyl peaks in its spectrum in tetrachloroethylene, four of which reached a maximum and then decreased, while the others continued to grow and finally (about 4 days) accounted for the total methyl absorption.

Repetition on a large scale and work-up gave a nearly quantitative yield of an isomer of **5a**, mp 200–201°; the same compound could be obtained more readily by refluxing either **5a** or equimolar amounts of **3** and and **4a** in bromobenzene for 5 hr. The uv absorption of the isomer at 284 nm (ϵ 13,000) was indicative of the conjugated α-methyl-β-phenyl cyclopentenone chromophore,[5] but the ir bands at 1768, 1740, and 1722 cm^{-1}, and the absence of absorption between 1720 and 1620 cm^{-1}, allowed confident rejection of the expected 1,3,4-oxadiazine structure **6a**. Absorption for C=N in the region 1680–1660 cm^{-1} has been well established for a number of oxadiazines derived from azo esters.[6]

While the uv and ir spectra were consistent with those predicted for the diazetidine **7a**, two features, in its nmr and its mass spectra, were not easily reconciled with the formulation **7a**. The nmr spectrum (CCl_4) had methyl peaks at τ 8.87, 7.90, 7.05, and 6.22, of which the first two and the last could be readily assigned to a *tert*-methyl, a vinyl methyl, and an ester methyl, respectively. The peak at τ 7.05, however, was at an unusually high field for any methoxy group. Furthermore, the high-resolution mass spectrum con-

(1) D. Mackay, J. A. Campbell, and C. P. R. Jennison, *Can. J. Chem.*, **48**, 81 (1970).

(2) J. A. Campbell, D. Mackay, and T. D. Sauer, *Can. J. Chem.*, **50**, 371 (1972).

(3) The adducts of dimethyl azodicarboxylate with cyclopentadiene and with 1,4-dimethyl-2,3-diphenylcyclopentadiene decompose slowly on heating at about 230 and 150°, respectively, but the reactions are complex. In each case several volatile products (gc) and colored high molecular weight material are formed; the total ir spectrum shows strong NH absorption.[4]

(4) D. Mackay, C. W. Pilger, and L. Wong, unpublished observations.

(5) C. F. H. Allen, T. Davis, D. W. Stewart, and J. A. VanAllan, *J. Org Chem.*, **20**, 310 (1955).

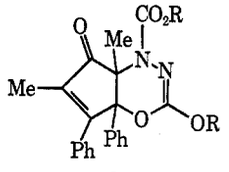
(6) J. Firl and S. Sommer, *Tetrahedron Lett.*, 1925, 1929 (1970); E. K. von Gustorf, D. V. White, B. Kim, D. Hess, and J. Leitich, *J. Org. Chem.*, **35**, 1155 (1970).

TABLE I

PREPARATION AND PROPERTIES OF ADDUCTS 5

Compd	Optimum time, hr	Mp, °C	ν (CCl_4),[a] cm^{-1}	τ (CCl_4) Ph[b]	τ (CCl_4) Ester	τ (CCl_4) C-Me
5a	24	119–120	1800, 1722, 1724	2.6–3.2	6.40 (Me)	8.20
5b	24	Glass	1800, 1744, 1718	2.6–3.2	5.90 (q, CH_2, J = 7.5 Hz) 8.97 (t, Me)	8.18
5c	2	Glass	1800, 1760, 1736	2.6–3.2	5.38 (AB q, CH_2, J = 12 Hz)	8.15
5d	1.5	Glass	1800, 1755, 1735	2.5–3.3	2.80 (Ph)[c]	8.05
5e	240	160–162	1800, 1732, 1716	2.6–3.2	8.65 (CMe_3)	8.26

[a] The 1800-cm^{-1} band is that of the bridging carbonyl. [b] Outer limits of absorption. [c] The sharp phenoxy peak dominates the broad phenyl pattern common to all the other adducts.



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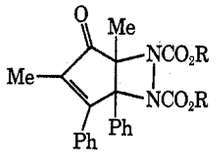

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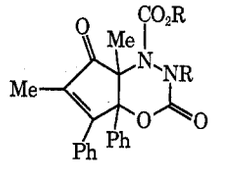

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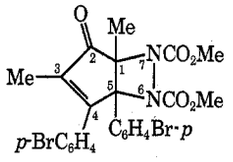


9

a, R = Me
b, R = Et
c, R = CH_2CCl_3
d, R = Ph
e, R = CMe_3

tained an intense peak (48% of the base peak) at m/e 275.1546 due to the oxygen-free ion $C_{19}H_{19}N_2^+$ which contained both nitrogen atoms and one methyl group from the original azo ester. Its occurrence was explicable only on the basis of a migration of methyl from oxygen to nitrogen or carbon during either the original isomerization of **5a** or the fragmentation of the product.

Both these spectroscopic observations were supportive of the presence of an *N*-methyl group in the isomer, a plausible structure being the 1,3,4-oxadiazin-2-one **8a**, which also fits the uv and ir data, and has credibility as the consequence of the expected[1,2] rearrangement of **5a** to **6a** (a hetero-Cope reaction), followed by a rapid [1,3] rearrangement of **6a** to **8a** (a modification of the Chapman[7] or the Chichibabin[8] rearrangement).

A decision between **7a** and **8a** was finally made on the basis of the X-ray analysis of the *p,p*-'dibromo analog. The synthesis of the latter involved the standard sequence[9,10] from *p,p'*-dibromobenzil to the dibromo derivative of the cyclone **3** (dimer, mp 180–182.5°), which was condensed with dimethyl azodicarboxylate to the dibromo derivative of **5a**. Isomerization in refluxing bromobenzene gave a product, mp 198.5–199.5°, whose spectra resembled those of the isomer of **5a** in all respects, including in particular a methyl absorption at τ 6.90 in its nmr and an abundant ion at m/e 432.9728 ($C_{19}H_{17}{}^{79}Br^{81}BrN_2^+$,) in its mass spectrum. X-Ray crystallography[11] showed this compound in fact to be the diazetidine **9**. Thus the stable end products of the isomerization of **5** are not the diazinones **8** but the diazetidines **7**.

In the crystal of **9** the methyl of the ester group on N-6 (see numbering scheme) is very close (*ca.* 3.4 Å) to the face of the phenyl ring on C-4.[11] If the assumption is made that the low-energy conformations in solution also have this ester group in a similar environment, the highly shielded absorption at τ 6.90 in **9** can be assigned to this methyl group.

The ion $C_{19}H_{19}N_2^+$ in the mass spectrum of **7a** has now recently been shown[4] to arise in a step involving decarboxylative migration of methyl from oxygen to nitrogen, and is an example of a general process in the fragmentation of cyclic bisurethanes, which may be formulated as $>NNCO_2R^+ \rightarrow RNN<^+ + CO_2$.

The diethyl adduct **5b** also gave a quantitative yield of the diazetidine **7b** on extended refluxing in tetrachloroethylene. The ditrichloroethyl adduct **5c**, however, gave an approximately equimolar yield of the diazetidine **7c** and the 1,2-dihydropyridazine ester **10c**, the product of decarbonylation; these were separated by fractional crystallization. The diphenyl adduct **5d** gave mainly the diazetidine **7d**, but a 10–15% yield of dihyropyridazine **10d** was evident in the nmr spectrum at the end of the reaction, though it was not isolated. The di-*tert*-butyl adduct **5e** gave only complex, tarry products on heating, among which neither **7e** nor **10e** could be positively identified. It appears that with the adducts derived from the azo esters of fairly acidic hydroxy compounds decarbonylation can compete with isomerization, but that bulky ester groups may inhibit both reactions.

The properties of the diazetidines **7a–d**, all of which were high-melting solids, are listed in Table II. The strong shielding of the ester group noted in **7a** and **9** takes an interesting form for the methylene group in **7b** and **7c**. Only one of the methylene protons is highly shielded in each case, and the resulting chemical shift differences in the pair, 0.92 ppm for **7b** and especially 1.98 ppm for **7c**, are remarkably large for geminal protons which are not part of a cyclic system. The simplest interpretation of this is that rotation of the methylene group is completely inhibited on the nmr time scale and that only one of the pair of protons is close to the face of the phenyl ring.[12]

(7) J. W. Schulenberg and S. Archer, *Org. React.*, **14**, 1 (1965); A. F. Hegarty, J. A. Kearney, M. P. Cashman, and F. L. Scott, *Chem. Commun.*, 689 (1971).

(8) R. A. Scherer and H. R. Beatty, *J. Org. Chem.*, **37**, 1681 (1972).

(9) F. R. Japp and J. D. Lander, *J. Chem. Soc.*, 123 (1897); F. R. Japp and J. Knox, *ibid.*, 673 (1905).

(10) F. W. Gray, *J. Chem. Soc.*, 2132 (1909).

(11) P. C. Chieh, D. Mackay, and L. Wong, *J. Chem. Soc., Perkin Trans. 2*, 2094 (1972).

(12) The line widths of the upfield protons are dependent on the field strength. This will be the subject of a forthcoming publication.

TABLE II

PREPARATION AND PROPERTIES OF DIAZETIDINES 7

Compd	Mp,[a] °C	ν (CCl_4),[b] cm^{-1}	λ_{max} (EtOH), nm (ϵ)	τ (CCl_4) Ph[c]	τ (CCl_4) Ester	τ (CCl_4) Vinyl Me	τ (CCl_4) *tert*-Me
7a	200–201	1768, 1740 1722	284 (13,000)	2.5–3.2	6.22 (Me), 7.05 (Me)	7.90	8.87
7b	178–179.5	1760, 1734 1720	282 (12,900)	2.5–3.2	5.73 (q, CH_2, J = 7.5 Hz), 6.10 (oct, H_A, AMX_3, J_{AX} = 7.5, J_{AM} = 10 Hz), 7.02 (oct, H_M), 8.70 (t, X_3, Me), 9.23 (t, Me)	7.93	8.83
7c	209–211	1778, 1750 1728	283 (13,300)	2.3–3.1	5.16 (AB q, CH_2, J = 12 Hz), 5.22 (d, H_A, AX, J_{AX} = 12 Hz), 7.20 (d, H_X)	7.88	8.69
7d	199–200	1778, 1750 1722	283 (13,500)	2.3–3.6		7.83	8.63

[a] **7a**, **7b**, and **7d** from methanol, **7c** from methanol–methylene chloride. [b] The first two peaks are due to the ester carbonyls, the third to the enone carbonyl. [c] Outer limits of absorption.

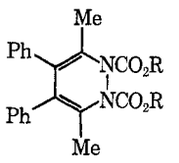
TABLE III

PREPARATION AND PROPERTIES OF OXIDIAZINES 6

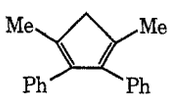
Compd	Time,[a] hr	Yield,[a] %	Mp, °C	ν (CCl_4),[b] cm^{-1}	λ_{max} (MeOH), nm (ϵ)	τ (CCl_4) Ph[d]	τ (CCl_4) Ester and alkoxy[e]	τ (CCl_4) Vinyl Me	τ (CCl_4) *tert*-Me
6a	55	60	151–152	1741, 1699 1675	282 (13,000)	2.5–3.0	6.15 (s, Me), 6.22 (s, Me)	7.75	9.05
6b	96	55	Glass	1745, 1700 1670	281 *c*	2.5–3.0	5.79 (q, CH_2), 5.87 (q, CH_2), 8.70 (t, 2 Me, J = 7.5 Hz)	7.85	9.06
6c	30	60	Glass	1748, 1715 1680	280 (13,600)	2.5–3.0	5.38 (broad s, 2 CH_2)	7.84	8.93
6d	24	60	161–162	1745, 1700 1685	284 (12,900)		2.5–3.1	7.78	8.82

[a] Optimum values, determined by nmr analysis during the reaction. [b] Peaks in order: ester C=O, enone C=O, C=N. [c] Intensity not determined. [d] Outer limits of absorption. [e] Not possible to say which is which. In $CDCl_3$ the methoxy peaks of **6a** are coincident.

The identities of the decarbonylation products **10c** and **10d** followed from their symmetrical nmr absorption pattern (methyl singlet near τ 7.8) and, for **10c**, the uv bands at 245 (ϵ 17,300) and 270–300 nm (broad shoulder, ϵ 4000 at 295 nm). Each of these bands is found separately in the model compounds, the diene **11** (240 nm, ϵ 18,000)[13] and the simple dihydropyridazine **12** (296 nm, ϵ 2900).[14] Their presence together is a powerful argument for structure **10** and precludes the alternative symmetrical 2,3-diazabicyclo[2.2.0] derivative **13**, whose chromophore would resemble that of *cis*-stilbene, and for which a good model exists[15] in the compound **14**, which absorbs strongly at 288 nm (ϵ 19,500).



10c, R = CH_2CCl_3
d, R = Ph



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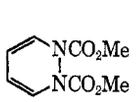

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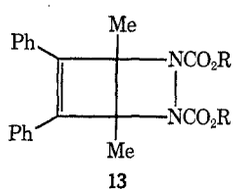

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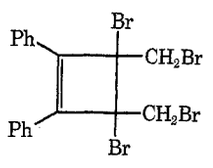

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The isomerization of **5a** was reexamined by nmr spectroscopy at various stages before completion. The four peaks due to the intermediate noted earlier reached a maximum in 8 days reflux in carbon tetrachloride, which accounted for 40–45% of the total reaction material. The optimum yield (60%) and its rate of attainment (2 days) were enhanced by the use of refluxing acetonitrile as solvent. Separation by silica gel chromatography at this point gave a compound, mp 151–152°, whose elemental analysis showed it also to be an isomer of **5a**. Its spectral properties included C=N ir absorption at 1675 cm^{-1} and almost coincident methoxy peaks[6] in its nmr spectrum near τ 6.2, consistent with its formulation as the oxadiazine **6a**, the product of [3,3] sigmatropic rearrangement of **5a**.

The oxadiazines **6b–d** were obtained similarly, the optimum yields and reflux times being listed with their spectral properties in Table III. Acetonitrile was for all of them the solvent of choice. The transition state to **6**, involving bond formation from benzylic carbon to oxygen, may be more sensitive to solvent polarity than the transition state to **7**, in which the bond is formed to nitrogen, since charge separation is likely to be more acute.

(13) P. Bladon, S. McVey, and P. L. Pauson, *J. Chem. Soc.*, 306 (1966).
(14) L. J. Altman, M. F. Semmelhack, R. B. Hornby, and J. C. Vederas, *Chem. Commun.*, 686 (1968).
(15) A. T. Blomquist and Y. C. Meinwald, *J. Amer. Chem. Soc.*, **81**, 667 (1959).

The relationship between **5**, **6**, and **7** was clarified by refluxing the oxadiazine **6d** in tetrachloroethylene and monitoring the reaction by nmr analysis.[16] Table IV, in conjunction with the above results, clearly shows

TABLE IV

PROPORTIONS[a] OF **6d**, **5d**, AND **7d** IN REFLUXING TETRACHLOROETHYLENE[b]

Reflux time, hr	6d	5d	7d
0	100	0	0
0.25	86	14	0
0.50	54	46	0
1.8	33	59	8
7.0	26	55	19
17.5	20	42	38
35.5	0	24	76
70.0	0	2	98
94.0	0	0	100

[a] Estimated per cent by nmr analysis. [b] 0.2 *M* total concentration.

that **5** and **6** are in reversible equilibrium with one another and that the former is transformed slowly into **7**. The conversion of **6** into **7** either does not occur at all or is very much slower than that of **5** into **7**.

The isomerization of **5** to **7** was readily reversed by photolysis. Good yields of **5** were rapidly obtained from benzene solutions of **7** at 10° using a 150-W mercury lamp and a Pyrex filter. The optimum times and yields are shown in Table V.

TABLE V

PHOTOISOMERIZATION OF **7** (3.3×10^{-3} *M*) TO **5** IN BENZENE AT 10°

Compd	Time, hr	Yield[a] of 5, %
7a	1.7	60–70
7b	3.0	55–65
7c	2.0	48–55
7d	20	75–80

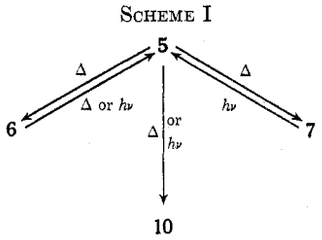
[a] Estimated by nmr analysis.

The oxadiazines **6** were stable to radiation above the Pyrex cut-off, but in quartz vessels their solutions in benzene were slowly isomerized, again to **5** (33% yield of **5a** after 30 hr, 43% of **5d** after 36 hr). The ROC=N chromophore, which must lie well below 300 nm, is presumably involved.

Both photolysis reactions were complicated by the instability of the product **5** to light, decarbonylation occurring to **10**.[17]

The generalized relationships between **5**, **6**, **7**, and **10** are indicated fully in Scheme I.

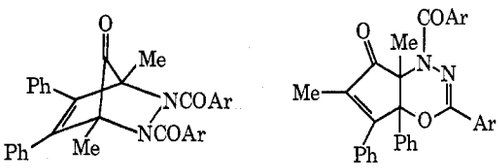
SCHEME I



(16) The areas of the *C*-methyl protons were used. This was the most suitable oxidiazine, since it had no other absorptions in the high-field region of the spectrum.

(17) The product from photolysis of **6c** or **7c** was identical with **10c** obtained by heating **5c**. This and other reactions of the bridging carbonyl group in **5** are being currently studied in detail.

The destabilizing influence of the keto bridge is also evident in the Diels–Alder adducts derived from azodiaroyls. The cyclone **3** and *p*,*p*′-dinitroazodibenzoyl in refluxing methylene chloride gave a quantitative yield of the oxadiazine **16a**, mp 191.5–192.5°, with methyl singlets at τ 7.85 and 8.77 and λ at 247, 281, and 335 nm, data which respectively exclude the symmetrical adduct **15a** and the isomeric diazetidine (the chromophore of *p*-$NO_2C_6H_4C{=}N$ occurs at 335 nm[2]) as possible structures. Azodibenzoyl gave a glassy adduct **16b** with analogous properties, including singlets at τ 7.90 and 8.57 in benzene; when the reaction was run in benzene at room temperature an additional methyl singlet at τ 8.00 was observed in the nmr spectrum in the early stages of the reaction, which reached a mazimum of about 10% of the total methyl absorption. This may be attributed to the intermediacy of **15b**,[18] which is thus an exceedingly labile species.



a, Ar = *p*-$NO_2C_6H_4$
b, Ar = Ph

Discussion

All the isomerizations of the 1,2-diazabicyclo compounds described above are formally sigmatropic processes: **5** ⇄ **6** and **15** → **16** are [3,3] rearrangements (transfer of bond between C to N and C to O) and **5** ⇆ **7** is a [1,3] rearrangement (transfer of N between C and C). Most have carbocyclic counterparts involving [2.2.1]- and [3.2.0]bicycloheptene derivatives. Of these the thermal [3,3] rearrangements (Cope type) are fairly common[19] but thermal [1,3] examples are rare.[20] When the rearrangements are concerted, and hence subject to orbital symmetry rules,[21] the constraints of the bicyclic molecular framework require a suprafacial shift for both components in the former type, through a boat-like transition state,[22] and a suprafacial migration of carbon with inversion of configuration in the latter.

Photo-Cope reactions like **6** → **5** have not been described for the analogous carbocyclic systems, though they are known for others,[24] but photo [1,3] rearrange-

(18) Enhancement of the concentration of **15b** (bimolecular reaction) over that of the thermal isomer **16b** (unimolecular reaction) would be achieved by a high concentration of reagents. However, the unfavorable dissociation of the cyclone dimer and its modest solubility militate against this.

(19) *E.g.*, R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959); P. Yates and P. Eaton, *Tetrahedron*, **12**, 13 (1961); R. C. Cookson, J. Hudec, and R. O. Williams, *J. Chem. Soc. C*, 1382 (1967); M. T. Hughes and R. O. Williams, *Chem. Commun.*, 587 (1968); I. R. Bellobono, P. Beltrame, M. G. Cattania, and M. Simonetta, *Tetrahedron*, **26**, 4407 (1970).

(20) J. A. Berson, *Accounts Chem. Res.*, **1**, 152 (1968).

(21) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

(22) Less favored than the chair-like transition state normally utilized in acyclic systems by a $\Delta\Delta G^{\ddagger}$ of 5.5–6 kcal/mol in the range 225–250°.[23]

(23) W. von E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962); M. J. Goldstein and M. S. Benzon, *J. Amer. Chem. Soc.*, **94**, 7147 (1972).

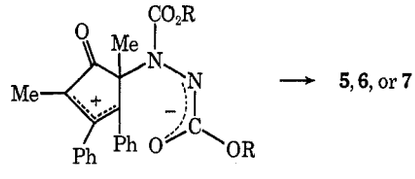
(24) O. L. Chapman and J. D. Lassila, *J. Amer. Chem. Soc.*, **90**, 2449 (1968); O. L. Chapman, M. Kane, J. D. Lassila, R. L. Loeschen, and H. E. Wright, *ibid.*, **91**, 6856 (1969); A. S. Kende, Z. Goldschmidt, and P. T. Izzo, *ibid.*, **91**, 6858 (1969); T. Sasaki, S. Eguchi, and M. Ohno, *ibid.*, **92**, 3193 (1970).

ments like 7 → 5 have ample precedent.[25] Most of these photoreactions are not concerted.

The application of orbital symmetry rules developed for carbocyclic systems to the thermal reactions of the heterocycles in the present work is of doubtful validity. In any event, these rules could not be utilized here as a proof of concertedness, since no stereochemical probe exists in any of these isomerizations to test them with. The [3,3] (hetero-Cope) rearrangements are confined by their geometry without stereochemical choice; the [1,3] rearrangement of 5 → 7 would involve, if concerted, inversion at the nitrogen, which is spontaneously rapid anyway.[26] Thus in the absence of other evidence (from kinetic and thermodynamic data or from trapping experiments) no conclusions can be drawn about the concertedness of the isomerizations.

The reacting frameworks in the isomerizations contain one kind (N) or two kinds (N and O) of heteroatom with nonbonded electron pairs, are substituted with charge and radical stabilizing groups (methyl, phenyl, acyl, or acyloxy) and experience a strong secondary interaction with the keto group.[28] Some of these features are evidently compatible with the operation of a concerted mechanism (though not necessarily one dictated by recognized orbital symmetry rules), as in the isomerization of 1 → 2 (R_1 = R_2 = H; R = Ph),[1] but the combination of all of them must greatly increase the likelihood of a stepwise mechanism.

A plausible intermediate in such a mechanism for the reversible processes of Scheme I is the dipolar species 17, ambident in both its cation and anion por-



→ 5, 6, or 7

tions, union of which in three of its four possible ways is observed in Scheme I. The driving force for its formation must lie particularly in the cation portion, namely, the stabilizing effect of the substituents and of the developing conjugation with the keto group, since the analogous adducts from cyclopentadiene are very stable.[3]

In the isomerization of the azodiaroyl adducts 15, though only a single, essential irreversible isomerization, to 16, is observed, a dipolar intermediate may still be involved (unlike the isomerization of the analogous adducts of cyclopentadiene, which are concerted[1]). The diazetidine isomeric with 15 and 16 may be thermodynamically less stable than either of them. The bulky *N*-aroyl groups would be sterically more demanding than the *N*-acyloxy groups of 7, which by virtue of the extra oxygen atom have a high degree of conformational flexibility and could allow the alkyl groups to occupy an uncrowded environment. Alternatively, or in addition, the inherent bond energy differences between isomeric oxadizines and diazetidines may weigh in favor of the former when derived from azodiaroyls and the latter when derived from azo esters.

Experimental Section

General Comments.—Melting points are uncorrected. Infrared spectra were recorded on a Beckman IR-10 and ultraviolet spectra on a Coleman EPS-3T Hitachi spectrometer. For the nuclear magnetic resonance spectra either a Varian T-60 or HA-100 instrument was used. Absorptions are quoted in τ values against tetramethylsilane as internal standard (abbreviations: s, singlet; d, doublet; t, triplet, q, quartet; m, multiplet). High-resolution mass spectra were obtained on a CEC21-110B or an AEI-MS9 spectrometer.

Azo Esters 4.—Di-2,2,2-trichloroethyl hydrazodicarboxylate was obtained from 2,2,2-trichloroethyl chloroformate by Rabjohn's method[33] (97%), and was recrystallized from aqueous ethanol, mp 101–102°. Oxidation with dinitrogen tetroxide[34] gave di-2,2,2-trichloroethyl azodicarboxylate, which crystallized as lemon-yellow plates (82%): mp 110–111° from benzene–hexane; ν (CCl_4) 1782 cm^{-1} (C=O); τ (CCl_4) 5.00 ppm (CH_2). This ester is stable indefinitely if stored in a desiccator in the dark.

Anal. Calcd for $C_6H_4Cl_6N_2O_4$: Cl, 55.86; N, 7.36. Found: Cl, 56.29; N, 7.41.

Dimethyl (4a), diethyl (4b), and diphenyl azodicarboxylate (4d) (orange plates, mp 122–123.5°, from benzene–hexane) were prepared similarly. Di-*tert*-butyl azodicarboxylate (4e) was purchased from Aldrich.

Cyclone 3.—Standard methods were used to convert 2,5-dimethyl-3,4-diphenyl-4-hydroxycyclopent-2-enone[9] to the dimer of 3[10] as well as to 1,4-dimethyl-2,3-diphenylcyclopentadiene.[13]

Dibromo Deivative of 3.—Condensation[35] of *p,p'*-dibromobenzil[36] with diethyl ketone gave 2,5-dimethyl-3,4-di-*p*-bromophenyl-4-hydroxycyclopent-2-enone. The mixture of epimeric carbinols was dehydrated[10] to the dimer of 1,4-dimethyl-2,3-di-*p*-bromophenylcyclopentadienone, which gave prisms, mp 180–182.5°, from methanol: ν (CCl_4) 1775, 1695 cm^{-1} (bridging, enone C=O); λ_{max} (EtOH) 236, 292 nm (ϵ 18,800, 13,500); nmr τ (CCl_4) 2.50–3.52 (m, 16, aromatic H), 7.88 (s, Me), 8.45 (s, Me), 8.83 (s, Me), 9.50 ppm (s, Me).

1,4-Dimethyl-5,6-diphenyl-2,3-carboalkoxy-2,3-diazabicyclo[2.2.1]hept-5-en-7-one (5) (See Table I).—The dimer of 3 (1.30 g, 2.5 mmol) and the azo ester 4 (5.01 mmol) were refluxed in carbon tetrachloride (40 ml), the progress of the reaction being monitored by nmr analysis, optimum yields of at least 90% being achieved. The solutions were then evaporated and worked up.

5a and 5d were crystallized from carbon tetrachloride in yields of 89 and 81%, respectively. 5a had λ_{max} (EtOH) 254 nm (shoulder, ϵ 9100).

Anal. Calcd for $C_{23}H_{22}N_2O_5$ (5a): C, 67.96; H, 5.46; N, 6.89. Found: 67.89; H, 5.49; N, 6.92.

5b, 5c, and 5d were noncrystalline. Each was purified by addition of hexane to an ethereal solution and allowing the gummy phase to settle out. The solvents were decanted and the residue was pumped *in vacuo* till it became brittle.

(25) L. S. Besford, R. C. Cookson, and J. Cooper, *J. Chem. Soc. C*, 1385 (1967); R. C. Cookson and D. C. Warrell, *ibid.*, 1391 (1967); R. L. Cargill, B. M. Gimarc, D. M. Pond, T. Y. King, A. B. Sears, and M. R. Willcott, *J. Amer. Chem. Soc.*, **92**, 3809 (1970).

(26) Amide nitrogen can be regarded as slightly pyramidal with rapid inversion and slow hindered rotation round the bond to the acyl group.[27]

(27) W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, **70**, 517 (1970), and references cited therein.

(28) As well as direct conjugation with the keto group present in 6 and 7 some interaction of the carbon–carbon double bond in 5 with the bridge is to be expected. Evidence for this in norborn-2-en-7-one is to be found in nmr,[29] ir,[30] uv,[31] and photoelectron[32] spectroscopy. Judging from the greater stability of 1 (R_1 = Ph; R_2 = Me; R = OMe)[3] than of 5 (R = Me), these interactions stabilize the transition state from 5 more than its ground state.

(29) Gurudata and J. B. Stothers, *Can. J. Chem.*, **47**, 3601 (1969).

(30) P. G. Gassman and W. M. Hooker, *J. Amer. Chem. Soc.*, **87**, 1079 (1965).

(31) R. E. Pincock and J. Hayward-Farmer, *Tetrahedron Lett.*, 4759 (1967); E. I. Snyder and B. Franzus, *J. Amer. Chem. Soc.*, **86**, 1170 (1964).

(32) D. Chadwick, D. C. Frost, and L. Weiler, *J. Amer. Chem. Soc.*, **93**, 4962 (1971).

(33) N. Rabjohn, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 375.

(34) J. C. Stickler and W. H. Pirkle, *J. Org. Chem.*, **31**, 3444 (1966).

(35) The use of Triton B as catalyst was an excellent variant on the usual aqueous sodium hydroxide.[9]

(36) H. Biltz, *Chem. Ber.*, **41**, 1761 (1908).

1,3-Dimethyl-4,5-diphenyl-6,7-dicarboalkoxy-6,7-diazabicyclo[3.2.0]hept-3-en-2-one (7) (See Table II). A.—The adducts **5** (5.0 mmol) were refluxed in tetrachloroethylene (40 ml) for 4 days, or, in the case of **5a**, in bromobenzene for 5 hr, and the solutions were then evaporated.

7a (>95% by nmr, 85% after crystallization) had *m/e* (rel intensity) 406.1522 (3, P^+, calcd 406.1524), 275.1546 (48, $C_{19}H_{19}N_2^+$, calcd 275.1558), 260.1196 (100, $C_{18}H_{16}O^+$, calcd 260.1201).

Anal. Calcd for $C_{23}H_{22}N_2O_5$: C, 67.96; H, 5.46; N, 6.89. Found: 67.86; H, 5.67; N, 7.04.

7b was obtained in >95% yield by nmr (85% after crystallization).

Anal. Calcd for $C_{25}H_{26}N_2O_5$: C, 69.11; H, 6.03; N, 6.45. Found: 69.27; H, 5.86; N, 6.42.

7c was obtained in *ca.* 50% yield by nmr (40% after crystallization). Addition of methanol (15 ml) caused separation of the crystalline diazetidine.

Anal. Calcd for $C_{25}H_{20}Cl_6N_2O_5$: Cl, 33.18; N, 4.37. Found: Cl, 32.95; N, 4.22.

7d was obtained in 85–90% yield by nmr (72% after crystallization).

7e could not be positively identified among the complex tarry products resulting from long heating of **5e** in tetrachloroethylene.

B. Alternate Synthesis of 7a.—A solution of the dimer of **3** (1.30 g, 2.5 mmol) and **4a** (0.73 g, 5.01 mmol) in bromobenzene (20 ml) was refluxed for 5 hr. Evaporation and crystallization of the residue from methanol gave **7a** (85%).

Ditrichloroethyl 3,6-Dimethyl-4,5-diphenyl-1,2-dihydropyridazine-1,2-dicarboxylate (10c).—The methanolic mother liquor from the separation of the crystalline diazetidine **7c** was reduced to half its volume and refrigerated for 24 hr. Crystalline **10c** separated as colorless prisms (34%): mp 123–124°; ν (CCl_4) 1740 cm^{-1}; λ_{max} (EtOH) 245 nm (ϵ 17,300) and broad shoulder (ϵ 4000 at 295 nm); nmr ($CDCl_3$) τ 3.0 (broad s, 10 phenyl H), 5.08 (AB q, 2 CH_2, J_{AB} = 12 Hz), 7.76 ppm (s, 2 Me).

Anal. Calcd for $C_{24}H_{20}Cl_6N_2O_4$: Cl, 34.69; N, 4.57. Found: Cl, 34.32; N, 4.56.

1,4-Dimethyl-5,6-di-*p*-bromophenyl-2,3-dicarbomethoxy-2,3-diazabicyclo[2.2.1]hept-5-en-7-one.—A solution of the dibromo derivative of **3** as its dimer (4.18 g, 5 mmol) and **4a** (1.46 g, 10 mmol) in carbon tetrachloride (250 ml) was refluxed for 30 hr, concentrated (50 ml), and refrigerated. The adduct slowly separated over 1 day, and was collected and recrystallized from carbon tetrachloride–pentane as prisms (80%): mp 111–113°; ν (CCl_4) 1800, 1750, 1725 cm^{-1} (bridging, ester C=O); nmr (CCl_4) τ 2.5–3.2 (m, q predominating, 8 aromatic H), 6.41 (s, OMe), 8.38 ppm (s, CMe).

Anal. Calcd for $C_{28}H_{20}Br_2N_2O_5$: Br, 28.37. Found: Br, 28.77.

1,3-Dimethyl-4,5-di-*p*-bromophenyl-6,7-dicarbomethoxy-6,7-diazabicyclo[3.2.0]hept-3-en-2-one (9). A.—The progress of the isomerization of the adduct (5.64 g, 10 mmol) in refluxing bromobenzene (40 ml) was monitored by nmr analysis of the methyl region. After 5 hr the two original methyl peaks had disappeared and the spectrum was consistent with the presence of the diazetidine **9** (85%) and a symmetrical compound (15%), perhaps the product of decarbonylation of the adduct. Evaporation and addition of methanol (15 ml) gave crystalline diazetidine which was recrystallized from ethanol as prisms: mp 198–199°; ν (CCl_4) 1770, 1741, 1723 cm^{-1} (two ester, enone C=O); λ_{max} (MeOH) 290 nm (ϵ 13,700); nmr ($CDCl_3$) τ 2.3–3.2 (m, 8, aromatic H), 6.20 (s, CO_2Me on N-7), 6.90 (s, CO_2Me on N-6), 7.90 (s, vinyl Me), 8.83 ppm (s, *tert*-Me); *m/e* (rel intensity) 564 (1, P^+ due to $C_{23}H_{20}{}^{79}Br^{81}BrN_2O_5^+$), 432.9728 (27, $C_{19}H_{17}{}^{79}Br^{81}BrN_2^+$, calcd 432.9738), 418 (100, due to $C_{19}H_{14}{}^{79}Br^{81}BrO^+$).

Anal. Calcd for $C_{23}H_{20}Br_2N_2O_5$: C, 48.94; H, 3.55; Br, 28.37; N, 4.97. Found: C, 48.70; H, 3.65; Br, 28.70; N, 5.08.

B.—The cyclone and the azo ester (1 mmol each) were refluxed in solution in bromobenzene for 7 hr. The solvent was removed and the solid residue was crystallized from methanol to give the diazetidine (85%), mp 198.5–199.5°.

***cis*-2-Alkoxy-4-carboalkoxy-4a,6-dimethyl-7,7a-diphenyl-4,4a,5,7a-tetrahydrocyclopenta-1,3,4-oxadiazin-5-one (6) (See Table III).** A.—A solution of **5a** (0.406 g, 1.0 mmol) was refluxed in carbon tetrachloride (6 ml) and the reaction was followed by nmr spectroscopy. A maximum yield (40–45%) of the desired product **6a** was obtained in about 8 days. With the same concentration in refluxing acetonitrile a maximum of 60% was obtained in 55 hr. Longer reflux times caused build-up of substantial amounts of **7a**.

The acetonitrile run was scaled up (10 mmol) and the solution was refluxed for 55 hr and evaporated. The residue was chromatographed on silica gel from petroleum ether (bp 60–80°)–ether (1:4). A small amount of the diazetidine **7a** was eluted first, then the main fraction, the oxidiazine **6a** (50%), and finally unreacted **5a**. Recrystallization of **6a** from ether–hexane gave prisms, mp 151–152°.

Anal. Calcd for $C_{23}H_{22}N_2O_5$: C, 67.86; H, 5.46; N, 6.89. Found: C, 67.54; H, 5.54; N, 7.07.

The remaining adducts were similarly refluxed in acetonitrile at the same concentrations, and the reaction products were purified by silica gel chromatography.

6b and **6c** were both glassy solids which resisted crystallization.

6d crystallized from petroleum ether (bp 30–60°)–carbon tetrachloride, mp 161–162°.

Anal. Calcd for $C_{33}H_{26}N_2O_5$: C, 74.70; H, 4.94; N, 5.28. Found: C, 74.42; H, 5.03; N, 5.56.

There was no conclusive evidence of the formation of **6e** after reflux for 8 days. The nmr spectrum of the substrate was very complex.

B. **Alternative Synthesis of 6a.**—The dimer of **3** (1.30 g, 2.5 mmol) and **4a** (0.73 g, 5 mmol) were refluxed in acetonitrile for 60 hr. Work-up and chromatography as before gave **6a** (50%).

Thermal Isomerization of 6d to 5d and 7d.—A solution of the oxadiazine **6e** (1.0 g, 1.9 mmol) in tetrachloroethylene (10 ml) was refluxed and periodically analyzed by nmr spectroscopy by noting the changes in the methyl group absorptions. The proportions were determined by repeated integration. The results are shown in Table IV.

Photochemical Reactions. A. Photoisomerization of 7 to 5.—The details for **7a** are typical. A solution of **7a** (0.203 g, 0.5 mmol) in dry benzene (150 ml), water-jacketed at 10°, was irradiated through Pyrex with a 125-W Hanovia uv immersion lamp. The reaction was followed by noting the appearance of the bridging carbonyl absorption at 1800 cm^{-1} in the ir and the methyl group absorption at τ 8.2 in the nmr spectrum, both characteristic of **5a**. After 100 min, the optimum time (60–70% yield by nmr analysis), the solution was evaporated and the residue was twice crystallized from carbon tetrachloride–pentane to give **5a**, mp 116–117°, alone or in admixture with authentic adduct.

Longer reflux times led to the appearance of a new methyl absorption in the nmr spectrum, attributable to the product of decarbonylation, **10a**.

The optimum times and yields for the photolysis of the other diazetidines **7b–d** are given in Table V.

When the photolysis of **7c** was extended to 6 hr, the solution evaporated, and the residue purified by chromatography on silica gel, the decarbonylated product **10c** was obtained as a glassy solid (40%). It slowly crystallized from methanol as colorless prisms, mp 123–124°, identical in all respects (spectra, mixture melting point) with the by-product in the thermal isomerization of **5c**.

B. Photoisomerization of 6 to 5.—The reaction was carried out only with the crystalline oxadiazines **6a** and **6d**. The scale, concentration, solvent, light source, and temperature were the same as in A. No reaction occurred over a period of many days when a Pyrex filter was used.

Isomerization occurred slowly in a quartz vessel, the bridging carbonyl and the methyl group of **5** being detectable as before. The optimum yield from **6a** was 30–35% after 30 hr. Evaporation and separation by silica gel chromatography (as described for the products from thermal isomerization of **5a**) gave **5a** identical in all respects with authentic adduct.

A 40–45% yield of **5d** was obtained from **6d** after 36 hr. The product was obtained directly by crystallization of the residue from carbon tetrachloride.

In either case longer reflux times led to decarbonylation of the product.

***cis*-2-Aryl-4-aroyl-4a,6-dimethyl-7,7a-diphenyl-4,4a,5,7a-tetrahydrocyclopenta-1,3,4-oxadiazin-5-one (16). A. 16a.**—A solution of the dimer of **3** (1.30 g, 2.5 mmol) and azodi-*p*-nitrobenzoyl[2] (1.64 g, 5 mmol) in methylene chloride (20 ml) was refluxed for

20 hr, and the solvent was evaporated. The residue had spectra essentially identical with those of **16a**, obtained by crystallization first from methanol–acetone, then from benzene–pentane, as pale yellow prisms (72%): mp 191.5–192.5°; ν (Nujol) 1730, 1683, 1652 cm^{-1} (enone, aroyl CO, C=N); λ_{max} (EtOH) 247, 281, 335 nm (ϵ 17,000, 23,200, 10,900); nmr ($CDCl_3$) τ 1.6–3.0 (m, 18, aromatic H), 7.85 (s, vinyl Me), 8.77 ppm (*tert*-Me).

Anal. Calcd for $C_{33}H_{24}N_4O_7$: C, 67.11; H, 4.44; N, 9.49. Found: C, 67.40; H, 4.56; N, 9.41.

B. 16b.—The reaction of the dimer of **3** (2.60 g, 5 mmol) with azodibenzoyl (2.38 g, 10 mmol) in refluxing benzene (50 ml) was monitored at 30-min intervals. After 10 hr the four methyl singlets of the dimer had been completely replaced by the two methyl singlets of **16b**, which was obtained as a glass, in high purity, on evaporation. An analytical sample was prepared by slowly adding hexane with stirring to a solution in benzene. The solvents were decanted and the residue on standing *in vacuo* became brittle; ν (CCl_4) 1732, 1665 cm^{-1} (enone and benzoyl C=O, C=N); λ_{max} (EtOH) 280 nm (ϵ 25,100); nmr (CCl_4) τ 2.0–3.2 (20, aromatic H), 7.85 (s, vinyl Me), 8.20 ppm (s, *tert*-Me).

Anal. Calcd for $C_{38}H_{26}N_2O_8$: C, 79.55; H, 5.26; N, 5.62. Found: C, 79.50; H, 5.40; N, 5.50.

A solution of the dimer of **3** and azodibenzoyl in benzene at the same concentration as above was kept at room temperature and the reaction was monitored by nmr analysis. As well as the two singlets at τ 7.90 and 8.57 due to the oxadiazine **16b**, a singlet was also evident at 8.00, attributable to **15b**, in the early stages of the reaction. It reached a maximum of about 10% of the total methyl absorption in 3 days.

Both **16a** and **16b** were stable to prolonged refluxing in bromobenzene.

Registry No.—**3** dimer, 38883-84-0; **3** *p*-bromophenyl dimer, 38883-85-1; **4a**, 2446-84-6; **4b**, 1972-28-7; **4c**, 38857-88-4; **4d**, 2449-14-1; **4e**, 870-50-8; **5a**, 38857-91-9; **5b**, 38857-92-0; **5c**, 38857-93-1; **5d**, 38857-94-2; **5e**, 38857-95-3; **6a**, 38864-11-8; **6b**, 38864-12-9; **6c**, 38864-13-0; **6d**, 38864-14-1; **7a**, 38857-96-4; **7b**, 38857-97-5; **7c**, 38857-98-6; **7d**, 38857-99-7; **9**, 38789-27-4; **10c**, 38858-01-4; **16a**, 38864-15-2; **16b**, 38864-16-3; di-2,2,2-trichloroethyl hydrazodicarboxylate, 38858-02-5; 1,4-dimethyl-5,6-di-*p*-bromophenyl-2,3-dicarbomethoxy-2,3-diazobicyclo[2.2.1]hept-5-en-7-one, 38858-03-6; azodi-*p*-nitrobenzoyl, 35630-50-3; azodibenzoyl, 959-31-9.

Acknowledgment.—We thank the National Research Council of Canada for support of this work.

Studies in the Imidazo[1,5-*a*]pyrazine System[1]

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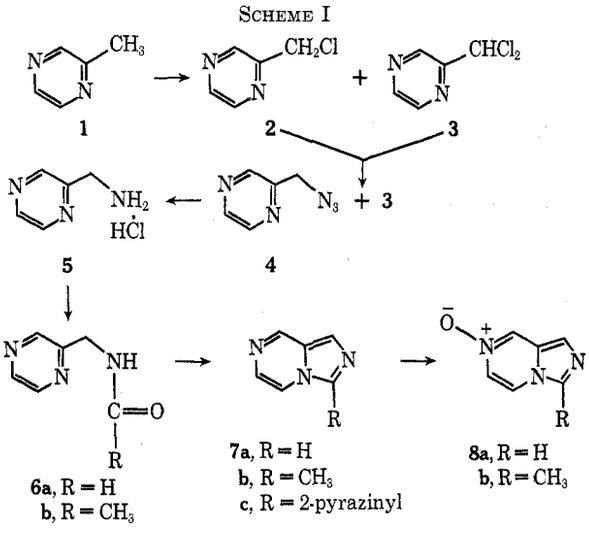
Received December 11, 1972

A general synthesis of imidazo[1,5-*a*]pyrazines as well as nmr studies on some derivatives is reported.

The first synthesis of an imidazo[1,5-*a*]pyrazine was reported recently using a novel reaction between pyrazine carboxaldehyde and ammonium chloride to give the 3-(2-pyrazinyl) derivative **7c**.[2] This method, however, cannot be used to prepare the parent heterocycle **7a** or alkyl-substituted derivatives such as **7b**, compounds in which we were interested as sources of imidazo[1,5-*a*]pyrazines that contained a variety of functional groups. This paper describes a general approach to such compounds and nmr studies that permit the identification of each of the protons in the heterocyclic system, an important consideration in assigning the structures of electrophilic substitution products of these heterocycles.

A key intermediate in our synthetic approach (Scheme I) was 2-aminomethylpyrazine. This rather unstable material has been reported previously derived from chloromethylpyrazine (**2**) using potassium phthalimide[3] but with very low yields, and this agrees with our observations of this method. We modified this procedure by utilizing the hydrolysis of the hexamine salt[4] prepared from **2** and hexamethylenetetramine, but again the yields were low and erratic. A practical route to **5** was available, however, by catalytic reduction of azidomethylpyrazine (**4**), which could be prepared,

SCHEME I



in good yield, from the reaction of **2** and sodium azide. Chloromethylpyrazine (**2**), prepared by the reaction of *N*-chlorosuccinimide with methylpyrazine (**1**),[5] was contaminated with dichloromethylpyrazine (**3**), which carries over as a contaminant in the formation of azide **4**. Pure **4** was obtained only after three distillations, in poor and impractical overall yield. Hydrogenation of the pure azide **4** furnished the amine, which was isolated as a hydrochloride salt (**5**) in 75% yield, but this repre-

(1) This work was carried out under the auspices of the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Public Health Service Contract No. NIH-71-2312.

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(3) A. Hirschberg and P. G. Mattner, *J. Med. Chem.*, **11**, 911 (1968).

(4) S. J. Angyal, *Org. React.*, **8**, 181 (1954).

(5) A. Hirschberg and P. E. Spoerri, *J. Org. Chem.*, **26**, 2356 (1961).