Application of Phenyl(trihalomethyl)mercurials in the Preparation of Heterocyclic Compounds[1,2]

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Pyrolysis of hydrazonodihalomethanes of type $(RO_2C)_2NN{=}CX_2$ (R = Me, Et; X = Cl, Br) resulted in formation, in high yield, of alkyl 5-halo-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylates. A different mode of decomposition was observed when R = Ph. The reaction of $PhHgCX_2Br$ (X = Cl and Br) with azodibenzoyl gave the respective benzoyl halide and 2-halo-5-phenyl-1,3,4-oxadiazole in a reaction that may have involved initial 1,4-addition of CX_2 to the N=NC=O system. Reaction of $PhHgCCl_2Br$ with $RO_2CN{=}C(CO_2Et)_2$ (R = Me or Et) resulted in formation of $ClCO_2R$ and the 2-chloro-4-carboethoxy-5-ethoxy-1,3-oxazole **16**. The possible mechanisms of these reactions are discussed.

In the previous paper of this series,[1] we reported concerning the reaction of phenyl(trihalomethyl)mercurials with azodicarboxylate esters (eq 1). We now report extensions of this research which have led to new preparative routes to heterocyclic compounds.

$$PhHgCX_3 + RO_2CN{=}NCO_2R \xrightarrow{80^\circ} PhHgX + \underset{\mathbf{1}}{(RO_2C)_2NN{=}CX_2} \quad (1)$$

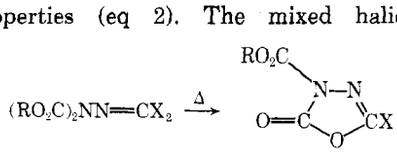
X = Cl, Br; R = Me, Et, Me_3C, $PhCH_2$, Ph

Results and Discussion

A. Preparation of Alkyl 5-Halo-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylates. Among the chemical conversions of the hydrazonodihalomethanes of type **1** which were examined at the time we were gathering chemical information relevant to the elucidation of their structure was their pyrolysis.

When the product of the reaction of $PhHgCCl_2Br$ and diethyl azodicarboxylate, $(EtO_2C)_2NN{=}CCl_2$, was heated at 200° for 1–2 hr, ethyl chloride was evolved and a high-boiling, colorless solid, mp 46–48°, was formed in high yield (80%). This product was very stable, surviving several hours of heating at 200–250°, and it could be purified by vacuum distillation and gas chromatography (glc). Its analysis indicated the composition $C_5H_5O_4N_2Cl$. Structure **2a** was compatible with most of the spectral features of this product (ir and ^{13}C nmr) except for the unusually high carbonyl frequency (1880 cm^{-1} in CCl_4) in its ir spectrum.[3]

Pyrolysis of those compounds of type **1** where R = CH_3 and C_2H_5 proceeded in similar fashion to give products believed to have structure **2** on the basis of their spectroscopic properties (eq 2). The mixed halide $(EtO_2C)_2$-NN=CClBr gave a 10:1 mixture of **2a** and **2b** on pyrolysis.

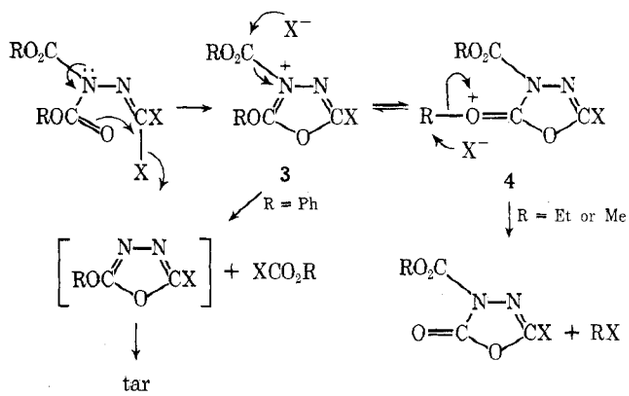


$$(RO_2C)_2NN{=}CX_2 \xrightarrow{\Delta} \mathbf{2} + RX \quad (2)$$

R = Et; X = Cl	**2a**, 80% yield
R = Et; X = Br	**2b**, 75% yield
R = Me; X = Cl	**2c**, 90% yield
R = Me; X = Br	**2d**, 94% yield

In contrast, the only volatile compound obtained from the thermolysis of $(PhO_2C)_2NN{=}CX_2$ was the phenyl haloformate (XCO_2Ph, X = Cl or Br), and a tarry residue remained. This may be understood in terms of an equilibrium established between immonium ion **3** and oxonium ion **4** intermediates (Scheme I). Alkyl-group stabilization of the oxonium ion would shift the equilibrium in favor of **4**.

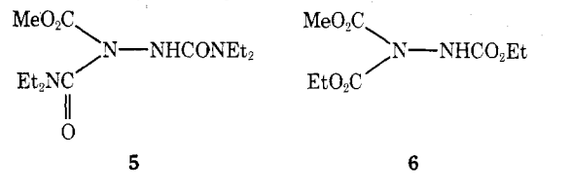
Scheme I



Elimination of RX (X = Cl or Br) from **4** would give a 1,3,4-oxadiazolinone. On the other hand, when R is phenyl, the stabilization of **4** is very much diminished, decomposition of immonium ion **3** becomes the main reaction course, and the phenyl haloformate is formed. The presumed 1,3,4-oxadiazoles formed in the latter reaction may not be stable under the reaction conditions and may undergo further reaction. In the thermolysis of $(PhCH_2O_2C)NN{=}CX_2$ (X = Cl or Br), a tarry residue and low yields of benzyl halides were obtained. It was not clear whether the benzyl halides were derived from the decomposition of **4** or from decarboxylation of benzyl haloformate initially formed in the decomposition of **3**. In the case of $(t\text{-}BuO_2C)_2NN{=}CX_2$, evolution of gas was observed, leaving an ill-defined solid residue which showed no apparent solubility in organic solvents or in water.

In order to confirm the proposed cyclic structure of **2a–d** and to obtain structural information which might serve to explain the spectroscopic properties, an X-ray crystal structure analysis of **2d** was undertaken. The results showed that the structure is indeed that assigned on the basis of spectroscopic evidence.[4]

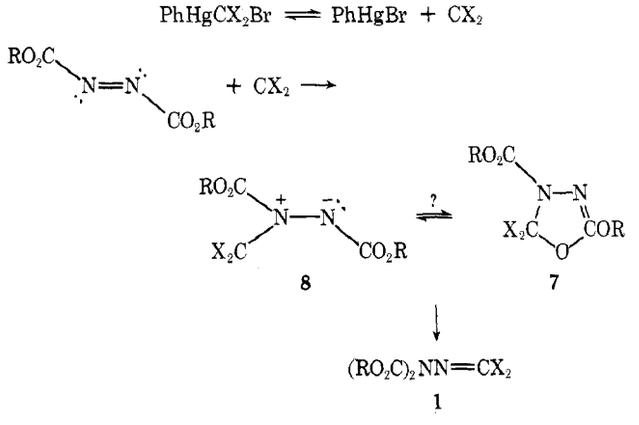
By this new route, new alkyl 5-halo-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylates are readily accessible. Their reactive carbon–halogen linkage may provide entry to other derivatives. For instance, as we have found, the C–Br bond of **2d** may be reduced to C–H by tri-*n*-butyltin hydride. Reaction of **2d** with diethylamine or ethanol gave ring-opened products, namely, the hydrazine derivatives **5** and **6**, re-



spectively. Acid hydrolysis of **2d** gave ethyl hydrazinecarboxylate, EtO_2CNHNH_2.

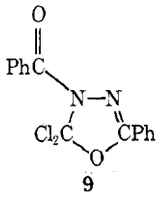
B. Preparation of Oxadiazoles and Oxazoles. The formation of compounds of type **1** in $PhHgCX_3$–$RO_2CN{=}NCO_2R$ reactions is believed to occur as shown in Scheme II.[1] An intermediate was isolated as a crystalline solid in the room-temperature reaction of $PhHgCBr_3$ with $MeO_2CN{=}NCO_2Me$. The spectral properties (ir and nmr) of this intermediate were interpreted as favoring the cyclic structure **7**, but did not exclude the open dipolar form **8**. If **7** is the correct structure of the intermediate, then its formation would involve a formal 1,4-addition of CX_2 to the $-N{=}NC{=}O$ system of the azodicarboxylate.

Scheme II



In general, carbenes add in a 1,2 fashion to C=C bonds of conjugated polyunsaturated systems of type >C=C–C=C< and >C=C–C=O,[5] rather than by 1,4-addition;[6] so possible 1,4-addition to $-N{=}N{-}C{=}O$ compounds merited further study. During the course of this investigation we found two types of compounds which reacted with $PhHgCX_3$ reagents to give stable heterocyclic products *via* apparent 1,4-addition reactions.

Azodibenzoyl might be expected to react with $PhHgCCl_2Br$ to give $(PhCO)_2NN{=}CCl_2$ as final product *via* intermediate **9** if the reaction course were the same

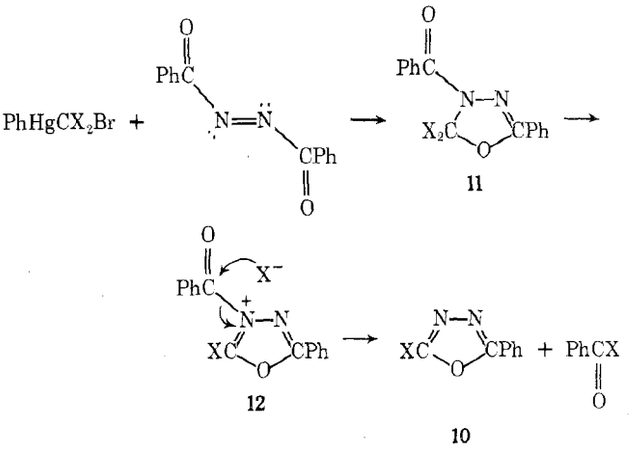


as that encountered in the $PhHgCCl_2Br$–$RO_2CN{=}NCO_2R$ reaction. Such, however, was not the case.

Reaction of $PhHgCCl_2Br$ with azodibenzoyl in benzene at 80° gave a complicated product mixture, presumably owing to the decomposition of azodibenzoyl; so the reaction was studied at room temperature. The mercurial and azodibenzoyl in CCl_4 were stirred at room temperature for 8 days and this was followed by a heating period of 1 hr at 80°. Two products, identified as benzoyl chloride and 2-chloro-5-phenyl-1,3,4-oxadiazole (**10**, X = Cl),[7] were obtained.

A spectroscopic study of the reaction by ir revealed that an intermediate with an ir band at 1610 cm^{-1} (probably a C=N vibration) had been formed and that this intermediate readily underwent further reaction at 80° to give the two observed products. Although the intermediate failed to crystallize, it very likely is a 1,3,4-oxadiazoline (**11**, X = Cl) as well, resulting from the 1,4(N,O)-addition of dichlorocarbene to azodibenzoyl *via* a mechanism similar to that postulated for azodicarboxylates. When $PhHgCBr_3$ was used instead of $PhHgCCl_2Br$, benzoyl bromide and bromo-1,3,4-oxadiazole (**10**, X = Br) were obtained. The products from these reactions possibly are derived from the dissociation of carbon–halogen bonds of the intermediate **11** to form an immonium salt **12** which then decomposes *via* nucleophilic attack of halide ion at the benzoyl carbonyl to give the benzoyl halide and **10**. Scheme III illustrates this possible mechanism.

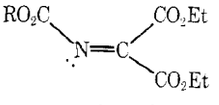
Scheme III



The quite different observed courses of the thermal reactions of **11** and **7** may be attributed to the presence of a better electrophilic carbonyl center (the benzoyl group) in **11**, which undergoes halide ion attack, resulting in elimination of benzoyl halide to give **10**.

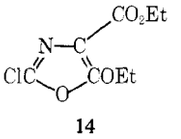
The yields of these novel oxadiazoles with a reactive halogen function, in these reactions were high enough (**10**, X = Cl, 54%; X = Br, 80%) to make these reactions preparatively useful. However, it was beyond the scope of this study to develop the potentially interesting C–X bond chemistry of **10**.

In view of these results with $-N{=}N{-}C{=}O$ compounds, it was of interest to extend this investigation to a compound containing an $-N{=}C{-}C{=}O$ system. Compounds of type **13** were chosen for further study.



13a, R = Et
b, R = Me

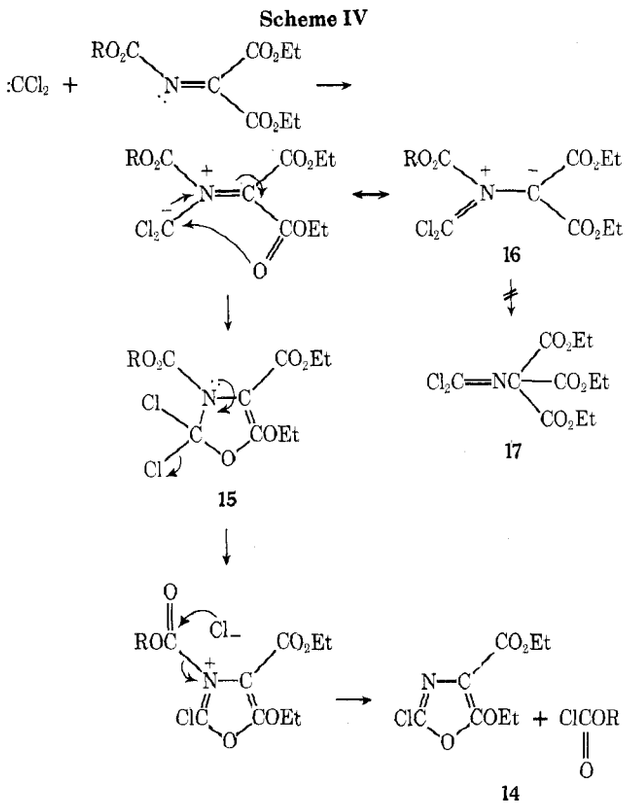
Reaction of $PhHgCCl_2Br$ with either the *N*-carboethoxyketimine **13a** or the *N*-carbomethoxyketimine **13b** at 80° in benzene solution gave one identical product in addition to ethyl chloroformate (R = Et) or methyl chloroformate (R = Me), depending on whether **13a** or **13b** was used. Apparently, the *N*-alkoxycarbonyl group was the one which was eliminated from the reaction intermediate to form the observed alkyl chloroformate. The analysis of the common product indicated the composition $C_8H_{10}ClNO_4$. The ^1H nmr spectrum of this product showed two nonequivalent OEt groups and its ir spectrum indicated the presence of C=O, C=C, and C=N functions by bands at 1720 s, 1620 s, and 1535 m cm^{-1}, respectively. The structure most compatible with these data is the 1,3-oxazole **14**.



A spectroscopic study of a $PhHgCCl_2Br$–**13b** reaction mixture after it had been stirred at room temperature for 4 days clearly indicated the formation of an intermediate by the ir absorption at 1630 cm^{-1} assignable to a C=C stretching vibration and its nmr signal for a OMe group at δ 3.86 ppm (this signal is differentiable from that of the $ClCO_2Me$ at δ 3.98 ppm). The same ir band at 1630 cm^{-1} was also observed when **13a** was used instead of **13b**, but in this case, the nmr spectrum of the OEt groups was too complex to analyze.

Although the intermediate was not isolated, in view of the final products obtained, **14** and $ClCO_2R$, as well as the spectral features, it is reasonable to believe that the 1,4(N,O)-addition of the dichlorocarbene to these ketimines to form **15** has also been achieved (Scheme IV). In Scheme IV, an azomethinimine intermediate **16** may or may not be involved. However, even if it had been formed, the bulky substituents on the carbanion center could prevent it from approaching the *N*-alkoxycarbonyl to realize the possible alkoxycarbonyl migration to give **17** *via* a mechanism similar to that proposed for the rearrangement of **8** to **7**.

Scheme IV



In these reactions also a novel heterocyclic product with a potentially reactive C–Cl bond has been formed. The yields of **14** were not high (20–35%), and the reaction study was not extended to include $PhHgCBr_3$, although one might expect better yields of product with this mercurial owing to the higher lability of a C–Br bond (*vs.* C–Cl) in an intermediate of type **15**.

Another reaction of $PhHgCCl_2Br$ was tried with >C=C–C=O type substrates, this time at room temperature rather than at 80°.[8] However, the reaction mixtures obtained after 6-day reactions with mesityl oxide and diethyl fumarate contained only the expected dichlorocyclopropanes, as seen by the nmr spectra of the reaction mixtures and by the subsequent isolation of the products.

Since the presence of a terminal nitrogen atom seems to facilitate 1,4-addition of CX_2 to α,β-unsaturated systems, we propose that the initial interaction between the substrate and CX_2 (or possibly with $PhHgCX_2Br$ rather than with free CX_2) occurs at the nitrogen atom and that this is followed by ring closure, as we have indicated. This 1,4-addition of CX_2 to –N=N–C=O and –N=C–C=O systems should be capable of further generalization and of application in the synthesis of heterocyclic systems containing halogen which are difficult to prepare by other routes.

Experimental Section

General Comments. All reactions were carried out in flame-dried glassware under an atmosphere of dry nitrogen. Solvents were carefully dried. Infrared spectra were recorded using a Perkin-Elmer Model 457A, 257, or 337B grating infrared spectrophotometer, ultraviolet spectra using a Cary-14 spectrophotometer, and proton nuclear magnetic resonance spectra using a Varian Associates T-60 or a Hitachi Perkin-Elmer R-20B high-resolution nmr spectrometer. Chemical shifts are expressed in δ units, parts per million downfield from tetramethylsilane. Carbon-13 nuclear magnetic resonance spectra were recorded using a Bruker HFX-90 nmr spectrometer interfaced with a Digilab NMR/FTS-3 Fourier transform data system. The carbon-13 chemical shifts are expressed in parts per million with respect to internal benzene. Mass spectra were recorded using a Hitachi Perkin-Elmer RMU-6 mass spectrometer. Gas–liquid partition chromatographs (glc) used were F & M Model 5754, 700, or 720 and M.I.T. isothermal units. Thin layer chromatography (tlc) was used to examine high-boiling reaction mixtures; Eastman silica gel tlc sheets, type 6061, were used.

Preparation of Starting Materials. Phenyl(bromodichloromethyl)mercury and phenyl(tribromomethyl)mercury were prepared by our THF method.[9] Azodibenzoyl, mp 118–119°, was prepared[10] by *N*-bromosuccinimide oxidation of *sym*-dibenzoylhydrazine (Aldrich). The reaction of diethyl ketomalonate with the respective *N*-carboalkoxy triphenylphosphinimine in THF at reflux[11] provided *N*-carboalkoxy diethyl ketomalonate ketimines. The *N*-carbomethoxy compound, $CH_3O_2CN{=}C(CO_2C_2H_5)_2$, is a new compound: bp 98–99° (0.08 mm); $n^{25}D$ 1.4391; ir (CCl_4) 2900 m, 1740 s, 1680 m, 1480 m, 1430 w, 1370 w, 1300 s, 1230 s, 1072 s, 1030 w, 910 w, 860 cm^{-1} w; nmr (CCl_4) δ 1.40 (t, 6, J = 7.0 Hz, OEt), 3.85 (s, 3, OMe), and 4.37 ppm (q, 4, J = 7.0 Hz, OEt).

Anal. Calcd for $C_9H_{13}NO_6$: C, 46.75; H, 5.67; N, 6.06. Found: C, 46.45; H, 5.82; N, 6.14.

The preparation of the $(RO_2C)_2NN{=}CX_2$ compounds whose thermolysis is reported was described in our previous paper in this series.[1]

Thermolysis of $(RO_2C)_2NN{=}CX_2$ Compounds. A. $(EtO_2C)_2NN{=}CCl_2$. The hydrazone (1.00 g, 3.80 mmol) was sealed in a Pyrex glass tube and heated at 180° for 1 hr. The resulting reaction mixture was a light yellow oil. After the tube was chilled in liquid nitrogen, it was opened and warmed up *slowly* to room temperature. The low-boiling material distilled and collected in a receiver at −78° at 1 atm (pot temperature to 30°) was a clear liquid which had an infrared spectrum identical with that of an authentic sample of ethyl chloride. The high-boiling product was isolated in 80% yield (0.60 g) by distillation at 0.02 mm (100°) as a colorless solid, mp 46–48°. An analytical sample was further purified by glc (6 ft × 0.25 in., 20% DC-200, 160°). The structure of the product was assigned as ethyl 5-chloro-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylate: ir (CCl_4) 2990 m, 1880 s, 1830 m, 1790 s, 1600 m, 1460 m, 1400 w, 1375 m, 1321 s, 1310 s, 1260 m, 1211 m, 1152 w, 1100 w, 1020 m, 925 m, 845 cm^{-1} w; ^1H nmr ($CDCl_3$) δ 1.42 (t, 3, J = 7.2 Hz, CH_3) and 4.40 ppm (q, 2, J = 7.2 Hz, CH_2); ^{13}C nmr ($CHCl_3$) −20.3 (C=O in CO_2Et), −19.9 (C=O in ring), −17.9 (C=N), 61.6 (CH_2), and 112.5 (CH_3) *vs.* benzene; mass spectrum (70 eV) *m/e* (rel intensity) 192 (1, M^+), 149 (3), 120 (25), 103 (13), 44 (17), 29 (100).

Anal. Calcd for $C_5H_5ClN_2O_4$: C, 31.18; H, 2.62; N, 14.55; Cl, 18.42. Found: C, 31.10; H, 2.87; N, 14.35; Cl, 18.20.

B. $(EtO_2C)_2NN{=}CBr_2$. Thermolysis of the hydrazone (1.00 g, 2.9 mmol) in a sealed tube at 180° for 30 min gave a brown reaction mixture. The tube was opened as described above. Distillation of the crude products gave one low-boiling compound which showed an infrared spectrum identical with that of an authentic sample of ethyl bromide and one high-boiling product (0.75 g, 75%). Further purification of the latter by glc (4 ft × 0.25 in., 10% UC-W98, 150°) yielded a white, crystalline substance, mp 52–53°, which was identified as ethyl 5-bromo-2-oxo-Δ^4-1,3,4-oxadiazo-

line-3-carboxylate: ir (CCl_4) 2980 w, 1870 s, 1816 m, 1781 s, 1580 m, 1560 w, 1390 w, 1370 m, 1316 s, 1300 s, 1240 m, 1200 s, 1140 m, 1090 w, 1015 m, 980 w, 915 m, 840 cm^{-1} w; nmr ($CDCl_3$) δ 1.44 (t, 3, J = 7.2 Hz, CH_3) and 4.52 ppm (q, 2, J = 7.2 Hz, CH_2).

Anal. Calcd for $C_5H_5BrN_2O_4$: C, 25.34; H, 2.20; N, 11.82; Br, 33.71. Found: C, 24.70; H, 2.13; N, 11.77; Br, 34.01.

C. $(EtO_2C)_2NN{=}CClBr$. Thermolysis of the hydrazone (0.5 g, 1.65 mmol) as described above gave a brown reaction mixture. Glc (4 ft × 0.25 in., 10% UC W98, 140°) analysis of the products showed that ethyl 5-chloro- and 5-bromo-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylate had been formed in a 10:1 ratio.

D. $(MeO_2C)_2NN{=}CCl_2$. The hydrazone (0.50 g, 2.20 mmol) was placed in a 5-ml, pear-shaped flask and heated at 180° for 30 min under a nitrogen atmosphere. After the reaction mixture was cooled to room temperature, a solid product formed. The crude product was purified twice by sublimation at 180° (100 mm) to give 3.50 g (90%) of colorless crystals, mp 107–109°, of methyl 5-chloro-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylate: ir (CCl_4) 3000 w, 2950 w, 1870 s, 1815 m, 1785 s, 1760 s, 1592 m, 1438 m, 1320 s, 1252 m, 1220 m, 1150 w, 1002 m, 915 cm^{-1} w; nmr ($CDCl_3$) δ 4.06 ppm (s).

Anal. Calcd for $C_4H_3ClN_2O_4$: C, 26.91; H, 1.69; N, 15.69; Cl, 19.86. Found: C, 26.77; H, 1.96; N, 15.11; Cl, 20.13.

E. $(MeO_2C)_2NN{=}CBr_2$. Thermolysis of the hydrazone (0.73 g, 2.30 mmol) in a flask at 160° for 20 min gave a light yellow liquid which solidified after cooling to room temperature. Purification of the product by sublimation at 90–100° (0.15 mm) gave 0.48 g (94%) of colorless crystals. Further recrystallization from chloroform gave nice hexagonal crystals, mp 119–120°. An X-ray crystal structure determination[4] confirmed the proposed structure of methyl 5-bromo-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylate: ir (CCl_4) 2980 w, 1910 w, 1870 s, 1790 s, 1580 m, 1437 m, 1330 w, 1310 s, 1240 m, 1210 m, 1142 m, 1000 w, 910 cm^{-1} w; nmr (CCl_4) δ 4.30 ppm (s).

Anal. Calcd for $C_4H_3BrN_2O_4$: C, 21.54; H, 1.35; N, 12.57; Br, 35.84. Found: C, 21.47; H, 1.61; N, 12.38; Br, 36.01.

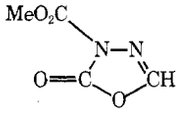
F. $(PhO_2C)_2NN{=}CCl_2$. Thermolysis of the hydrazone (0.70 g, 2.0 mmol) at 200° for 30 min gave a black reaction mixture. Distillation of the mixture at 60–70° (0.30 mm) gave a colorless distillate (0.20 g, 67%) and a tar residue. The volatile compound was identified as phenyl chloroformate, ir (neat) 3060 w, 1780 s, 1590 m, 1490 s, 1461 m, 1172 s, 1160 s, 1120 s, 1070 w, 1020 w, 1012 m, 856 s, 745 s, 680 s, 580 s, 500 cm^{-1} m, which is identical with the Sadtler Standard Spectrum No. 13473 of authentic phenyl chloroformate.

G. $(PhO_2C)_2NN{=}CBr_2$. When this hydrazone (0.50 g, 1.14 mmol) was thermolyzed at 190° for 30 min, a similar black reaction mixture was obtained. The only volatile compound (0.14 g, 50%) isolated by distillation at 80–90° (0.30 mm) was identified by ir spectrum (neat, 3060 w, 1780 s, 1588 s, 1460 w, 1282 w, 1170 s, 1150 s, 1120 s, 1025 w, 1000 m, 912 m, 840 s, 740 s, 685 s, 640 m, 562 m, 498 cm^{-1} m) as phenyl bromoformate.

H. $(PhCH_2O_2C)_2NN{=}CCl_2$. This hydrazone (0.50 g, 1.32 mmol) was heated at 200° for 30 min to give a black reaction mixture. The only volatile compound found by distillation (80–90°, 0.01 mm) was benzyl chloride (0.06 g, 33%). The product was identified by the comparison of its ir spectrum with that of an authentic sample from Aldrich.

Benzyl bromide was the only volatile product of the pyrolysis of $(PhCH_2O_2C)_2NN{=}CBr_2$.

Reduction of Methyl 5-Bromo-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylate. The oxadiazolinone (0.35 g, 1.56 mmol) and tri-*n*-butyltin hydride (0.47 g, 1.60 mmol) were heated at 80° for 4 hr. The starting compound completely dissolved on heating while the reduced product precipitated when it was formed. The reaction mixture was cooled in an ice bath and then filtered from the solid product. The product, after recrystallization from acetone at −78°, was a colorless solid, mp 85–87°, 0.17 g (75% yield). The compound was identified as methyl 2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylate: ir (CCl_4) 3125 w, 3002 w, 2950 w, 1910 w, 1840 s, 1780 s, 1595



m, 1435 m, 1340 s, 1320 s, 1285 w, 1220 m, 1160 w, 1105 m, 1000 m, 905 cm^{-1} w; nmr ($CDCl_3$) δ 4.10 (s, 3, CH_3) and 7.68 ppm (s, 1, N=CH).

Anal. Calcd for $C_4H_4N_2O_4$: C, 33.34; H, 2.80; N, 19.45. Found: C, 33.27; H, 3.02; N, 19.56.

Reaction of Methyl 5-Bromo-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylate with Diethylamine. The oxadiazolinone (0.50 g, 2.0 mmol) in 2 ml of tetrahydrofuran was treated dropwise with 0.15 g (2.0 mmol) of diethylamine at 0–5°. Immediate formation of a white precipitate was observed. Glc analysis (M.I.T. isothermal unit, 4 ft × 0.25 in., 10% SE-30, at 150°) of the solution showed that one high-boiling product had formed and that most of the starting material remained intact. An additional 0.45 g (6.00 mmol) of diethylamine was added to complete the reaction. The reaction mixture was filtered from the precipitate of $Et_2NH{\cdot}HBr$, and the filtrate was examined by glc. The same high-boiling product found above was the sole reaction product. The product, **5**, was isolated by glc: ir (CCl_4) 3290 m, 2970 m, 1730 s, 1660 s, 1430 m, 1330 m, 1310 w, 1260 s, 1220 w, 1160 w, 1100 m, 850 cm^{-1} w; nmr (CCl_4) δ 1.18 (t, 3, J = 7.1 Hz, CH_2CH_3), 1.20 (t, 3, J = 7.1 Hz, CH_2CH_3), 3.27 (q, 2, J = 7.1 Hz, CH_2CH_3), 3.36 (q, 2, J = 7.1 Hz, CH_2CH_3), 3.50 (s, 3, OCH_3), and 8.39 (s, 1, NH).

Anal. Calcd for $C_{12}H_{24}N_4O_4$: C, 49.98; H, 8.39; N, 19.43. Found: C, 50.18; H, 8.25; N, 19.93.

Ethanolysis of Ethyl 5-Chloro-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylate. The 1,3,4-oxadiazolinone (0.10 g) was treated with 3 ml of 95% ethanol at room temperature for 20 hr. The resulting reaction mixture was examined by glc (4 ft × 0.25 in., 10% UC W98, 160°) which showed that all the starting material had been converted to 1,1,2-tricarboethoxyhydrazine. The product was identified by comparison of its glc retention time and ir spectrum to those of the authentic compound obtained in a previous reaction.[1]

Acid Hydrolysis of Ethyl 5-Chloro-2-oxo-Δ^4-1,3,4-oxadiazoline-3-carboxylate. The oxadiazolinone was treated with 2 *N* hydrochloric acid at 80° for 1 hr. The reaction mixture was neutralized with 2 *N* sodium hydroxide solution and then extracted with ether. The product, isolated from the dried organic layer by glc (4 ft × 0.25 in., 10% UC W98, 130°), showed an identical glc retention time and ir spectrum with those of authentic carboethoxyhydrazine, EtO_2CNHNH_2 (obtained from Aldrich).

Reaction of Phenyl(bromodichloromethyl)mercury with Azodibenzoyl. The azo compound (1.30 g, 5.00 mmol), the mercurial (2.20 g, 5.00 mmol), and 10 ml of carbon tetrachloride were placed in a 25-ml flask and stirred at room temperature under a nitrogen atmosphere. The progress of the reaction was monitored by ir spectroscopy. After a 3-day reaction period, an initial reaction product formed as indicated by new ir bands at 1775 s, 1610 s, 1580 w, 1060 s, and 960 cm^{-1} m. The reaction was discontinued at the end of 8 days. At this time, the reaction mixture showed additional new ir bands at 1780 sh, 1500 w, 1488 w, 1195 w, and 870 cm^{-1} m. The mixture was filtered from phenylmercuric bromide and unconverted starting mercurial and the filtrate was evaporated to dryness, leaving an oily residue and some solid. The oil contained mainly the initial reaction product as indicated by its ir spectrum. Attempted isolation of the initial product by recrystallization from acetone or ether at −78° failed. However, heating this oil at 80° for 1 hr gave two products, one a solid, the other a liquid. The latter was separated by filtration, and its further purification by glc showed an identical glc retention time and ir spectrum with those of an authentic sample of benzoyl chloride. The crude solid was recrystallized from carbon tetrachloride to give colorless crystals of 2-chloro-5-phenyl-1,3,4-oxadiazole, mp 76–78° (lit.[7] mp 75°). The spectral properties which were not reported are shown below: ir (CCl_4) 3060 w, 1970 w, 1955 w, 1910 w, 1890 w, 1810 w, 1760 w, 1740 m, 1607 w, 1590 w, 1550 m, 1498 s, 1450 m, 1370 w, 1330 w, 1285 w, 1196 s, 1178 w, 1075 w, 1064 s, 1028 m, 1008 m, 960 m, 950 m, 922 w, 708 s, 690 cm^{-1} s; nmr (CCl_4) δ 7.50 (m, 3) and 8.00 ppm (m, 2); mass spectrum (70 eV) *m/e* (rel intensity) 182 (12), 180 (36), 145 (33), 126 (9), 124 (27), 105 (73), 103 (37), 96 (20), 95 (5), 93 (4), 89 (21), 86 (13), 84 (24), 78 (7), and 77 (100).

Reaction of Phenyl(tribromomethyl)mercury with Azodibenzoyl. A 50-ml flask was charged with the azo compound (2.30 g, 9.80 mmol), the mercurial (10.0 g, 19.0 mmol), and 30 ml of carbon tetrachloride. The reaction mixture was stirred at room temperature for 5 days. The resulting mixture was a light yellow solution whose ir spectrum showed the formation of the initial reaction product as indicated by bands at 1775, 1755, 1610, 1576, 1485, 1170, 1060, and 952 cm^{-1}. The reaction mixture was filtered from phenylmercuric bromide and unconverted mercurial. The filtrate was then washed with 5% aqueous sodium sulfide solution and water. The dried organic layer was evaporated to dryness to give 1.20 g (30%) of oily products. Attempted crystallization of the oil at low temperature (−78°) failed. The oil was redissolved in carbon tetrachloride and refluxed for 1.5 hr. When the reaction was followed by ir spectroscopy, an increase in the intensities of ir bands at 1775, 1485, 1170, and 825 cm^{-1} at the expense of the

bands due to the initial product at 1755, 1610, 1575, and 1060 cm^{-1} was observed. Glc (4 ft × 0.25 in., UC W98, 160°) analysis of the resulting solution showed that two products had been formed in 1:1 ratio. The low-boiling product, isolated by glc, was found to be benzoyl bromide, identified by the comparison of its glc retention time and ir spectrum to those of the authentic compound (Aldrich). Colorless crystals of the second product (0.23 g, 80% based upon the initial reaction product) were obtained from carbon tetrachloride solution at 0°. Further recrystallization from carbon tetrachloride at 0° gave colorless needles, mp 107–109°. The compound was identified as 2-bromo-5-phenyl-1,3,4-oxadiazole: ir (CCl_4) 3060 w, 1975 w, 1955 w, 1910 w, 1890 w, 1770 m, 1610 w, 1550 m, 1485 s, 1450 m, 1340 w, 1320 w, 1170 s, 1075 sh, 1060 m, 1025 w, 995 w, 958 w, 950 w, 925 w, 850 w, 710 m, 690 cm^{-1} m; nmr (CCl_4) δ 7.52 (m, 3) and 8.00 ppm (m, 2).

Anal. Calcd for $C_8H_5BrN_2O$: C, 42.69; H, 2.24; N, 12.45; Br, 35.31. Found: C, 42.62; H, 2.32; N, 12.29; Br, 35.20.

Reaction of *N*-Carboethoxy Diethyl Ketomalonate Ketimine with Phenyl(bromodichloromethyl)mercury. The imine (2.45 g, 10.0 mmol), phenyl(bromodichloromethyl)mercury (4.40 g, 10.0 mmol), and 10 ml of benzene were stirred and heated at reflux under a nitrogen atmosphere for 2 hr. The resulting reaction mixture was filtered from 2.80 g (80%) of white, crystalline phenylmercuric bromide, mp 270–272°. Glc analysis of the filtrate (M.I.T. isothermal unit, 10% SE-30, 4 ft × 0.25 in., 145°) showed the presence of a large quantity of the unconverted starting imine and one product having a shorter glc retention time than that of the imine. Because of the presence of the big portion of the imine, isolation of the product from the reaction mixture by glc was not feasible. Therefore, the crude product obtained after evaporation of the solvent was column chromatographed (neutral alumina column). The product was easily eluted while the imine remained on the column. The analytical sample was further purified by glc (4 ft × 0.25 in., UC W98, 140°), $n^{25}D$ 1.4833. The structure was assigned as 2-chloro-4-carboethoxy-5-ethoxy-1,3-oxazole (**14**): ir (neat) 2900 m, 1720 s, 1620 s, 1535 m, 1380 w, 1350 w, 1250 m, 1170 s, 1060 s, 1000 w, 890 w, 860 w, 840 w,780 m, 650 cm^{-1} w; nmr (neat) δ 1.16 (t, 3, J = 7.1 Hz), 1.29 (t, 3, J = 7.1 Hz), 4.05 (q, 2, J = 7.1 Hz), and 4.38 ppm (q, 2, J = 7.1 Hz) due to OEt groups.

Anal. Calcd for $C_8H_{10}ClNO_4$: C, 43.75; H, 4.59; N, 6.38; Cl, 16.15. Found: C, 43.54; H, 4.60; N, 6.09; Cl, 16.21.

The imine (1.30 g, 5.00 mmol), the mercurial (2.20 g, 5.00 mmol), and 8 ml of benzene were stirred and heated at reflux for 3 hr. Glc (M.I.T. isothermal unit, 4 ft × 0.25 in., 20% SE-30, 155°, *n*-tridecane internal standard) analysis of the resulting reaction mixture showed that **14** was present in 28% yield (1.40 mmol). When additional 2.20 g of the mercurial was added and the mixture was refluxed for another 3 hr, the yield of **14** was found to be 15%. In another run using a threefold excess of the mercurial, the yield of **14** was found to be 14%. When equimolar amounts of the mercurial and the imine (5.00 mmol each) in 5 ml of benzene were stirred at room temperature for 12 days, the yield of **14** was 18%.

Attempted detection of ethyl chloroformate formed in the above reactions in benzene solution failed because the compound has a very close glc retention time to that of the solvent. Therefore, the reaction was run without solvent. The imine (2.54 g, 10.0 mmol) and the mercurial (2.20 g, 5.0 mmol) were placed in an 25-ml, pear-shaped flask equipped with a reflux condenser topped with a vacuum distillation head with a receiver chilled in a Dry Ice–acetone bath. The reaction mixture was stirred and heated at 85° (100 mm) for 3 hr. The low-boiling (0.10 g, 20%) product which collected in the receiver was a colorless liquid and was identified as ethyl chloroformate by comparison of its ir spectrum with that of an authentic sample (Aldrich). The reaction product **14** was formed in 35% yield in this reaction, and 7.0 mmol of the starting imine was recovered.

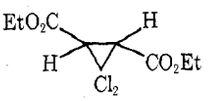
Reaction of *N*-Carbomethoxy Diethyl Ketomalonate Ketimine with Phenyl(bromodichloromethyl)mercury. The imine (2.30 g, 10.0 mmol), the mercurial (4.40 g, 10.0 mmol), and 10 ml of benzene were stirred and heated at reflux for 3 hr. The reaction mixture was filtered from 3.0 g (85%) of white phenylmercuric bromide, mp 263–265°. Glc (M.I.T. isothermal unit, same column and conditions used above) analysis of the filtrate showed one product peak which overlapped with the starting imine peak. The product showed an identical glc retention time with that of the product obtained from the *N*-carboethoxy imine reaction and was purified by column chromatography (neutral alumina). Its glc retention time and spectra (ir and nmr) were identical with those of **14**. The yield determined by glc (M.I.T. isothermal unit, 4 ft × 0.25 in., 10% SE-30, 155°) was found to be 15% (0.15 mmol).

Spectroscopic Study of the Reaction of *N*-Carbomethoxy Diethyl Ketomalonate Ketimine with $PhHgCCl_2Br$ at Room Temperature. When the imine (1.0 g, 5.0 mmol) and the mercurial (2.00 g, 5.0 mmol) in 5 ml of CCl_4 were stirred at room temperature for 4 days, the ir spectrum of the reaction mixture showed a new band at 1630 cm^{-1} assignable to a C=C stretching vibration. Its nmr spectrum showed new resonances (singlets) at δ 3.86 and 3.98 ppm. The latter was most likely due to the OMe signal of the methyl chloroformate, since this signal was enhanced when $ClCO_2Me$ was added to the reaction mixture. After 12 days, the nmr signal of the reaction mixture at 3.86 ppm disappeared. The ir band at 1630 cm^{-1} and nmr resonance at 3.86 ppm were most likely due to the reaction intermediate **15** (R = Me), which can rearrange to the observed final products, **14** and $ClCO_2Me$, at room temperature. The nmr signals of OEt groups were too complex to analyze.

The reaction mixture of $PhHgCCl_2Br$ (4.40 g, 10.0 mmol) and $(EtO_2C)N{=}C(CO_2Et)_2$ (2.45 g, 10.0 mmol) in 10 ml of CCl_4 at room temperature for 2 days also showed the new ir band at 1630 cm^{-1}. However, its nmr spectrum was too complex to analyze.

Reaction of Diethyl Fumarate with $PhHgCCl_2Br$. Diethyl fumarate (1.74 g, 10.0 mmol) and the mercurial (4.00 g, 9.8 mmol) in 10 ml of CCl_4 were stirred at room temperature for 6 days. The nmr spectrum of the reaction mixture showed one new resonance at δ 2.96 ppm (singlet) which is most likely due to the cyclopropyl CH protons. The OEt signal of the product was hardly distinguishable from that of the starting olefin. Its ir spectrum showed no band other than the C=C vibration of the starting olefin. Therefore, the 1,4-addition of the CCl_2 to a C=C–C=O conjugated system of diethyl fumarate was not realized.

The reaction mixture was heated at 80° for 2 hr, and then was filtered from 3.00 g (85%) of PhHgBr, mp 265–269°. The filtrate was trap-to-trap distilled (100°, 0.02 mm) and the product was isolated by glc (4 ft × 0.25 in., 10% UC-W98, 145°) in 31% yield (3.04



mmol): $n^{25}D$ 1.4611; ir (neat) 3022 w, 2980 m, 2940 w, 2900 w, 1740 s, 1460 w, 1440 w, 1372 w, 1366 m, 1310 s, 1260 m, 1180 s, 1090 w, 1060 m, 1030 m, 980 m, 970 w, 940 m, 930 m; nmr (neat) δ 1.25 (t, 6, J = 7.5 Hz, CH_3), 4.20 (q, 4, J = 7.5 Hz, CH_2), and 2.96 ppm (s, 2, cyclopropyl CH).

Anal. Calcd for $C_9H_{12}Cl_2O_4$: C, 42.37; H, 4.74; Cl, 27.80. Found: C, 42.83; H, 4.92; Cl, 27.46.

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Registry No.—1 (R = Et; X = Cl), 36133-63-8; 1 (R = Et; X = Br), 51381-28-3; 1 (R = Et; X = Br + Cl), 51381-32-9; 1 (R = Me; X = Cl), 51381-23-8; 1 (R = Me; X = Br), 51381-27-2; 1 (R = Ph; X = Cl), 51381-26-1; 1 (R = Ph; X = Br), 51381-31-8; **1** (R = Ph; X = Cl), 51381-25-0; **2a**, 36133-66-1; **2b**, 51806-26-9; **2c**, 51806-27-0; **2d**, 38658-91-2; **2** (r , me; X = H), 51806-28-1; **5**, 51806-29-2; **10** (X = Cl), 1483-31-4; **10** (X = Br), 51039-53-3; **13a**, 36106-23-7; **13b**, 51039-55-5; **14**, 51039-54-4; diethyl ketomalonate, 609-09-6; *N*-carbomethoxytriphenylphosphinimine, 40438-23-1; phenyl bromoformate, 51806-30-5; phenyl (bromodichloromethyl)mercury, 3294-58-4; azodibenzoyl, 959-31-9; phenyl(tribromomethyl)mercury, 3294-60-8; diethyl fumarate, 623-91-6; diethyl *trans*-3,3-dichlorocyclopropane-1,2-dicarboxylate, 51806-31-6.

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Hydrogen Cyanide Chemistry. VIII. New Chemistry of Diaminomaleonitrile. Heterocyclic Synthesis[1]

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Alkyl derivatives of diaminomaleonitrile (DAMN), are prepared by direct methylation and by reduction of Schiff bases. Cyclic anhydrides and DAMN produce amide acids. 2,3-Dicyanodiazepines and 2,3-dicyanodihydrodiazepines are prepared by condensation of DAMN with 1,3-diketones or other carbonyl derivatives. 2-Substituted 4,5-dicyanoimidazoles are prepared by improved cyclization procedures of Schiff bases and amides of DAMN. Tetrasubstituted pyrazines are prepared by condensation of DAMN with diimines prepared from alcohols and cyanogen.

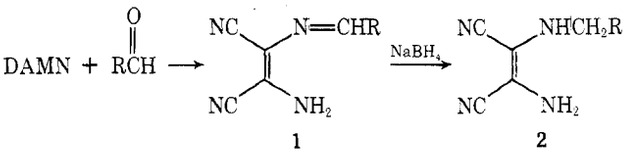
Diaminomaleonitrile (DAMN), a weakly basic diamine resembling *o*-phenylenediamine in reactivity, can be prepared directly from hydrogen cyanide by oligomerization[2] and indirectly by hydrogenation of diiminosuccinonitrile.[3] DAMN has been proposed to be an essential intermediate to purines in prebiotic origin of life[4] and has been used to prepare a variety of heterocyclic compounds, including 4,5-dicyanoimidazoles,[5,6] 5,6-dicyanopyrazines,[1,7] and purines[8] (including caffeine[5]), as well as amides[5,7a,9] and Schiff bases.[7a,9] We now report synthesis of new alkyldiaminomaleonitriles and seven-membered diazaheterocycles from DAMN; also we have extended the synthesis of five- and six-membered heterocycles and Schiff bases from DAMN.

Results and Discussion

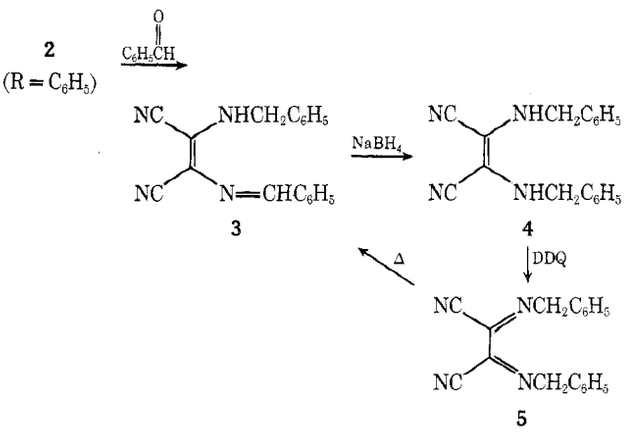
Schiff Bases of Diaminomaleonitrile. DAMN condenses rapidly with aliphatic and simple aromatic aldehydes in methanol without a catalyst.[7a,9] However, if the aldehyde is substituted by a strong electron-withdrawing group, acid catalysis (sulfuric acid) is required to make the condensation proceed at a reasonable rate. For amides, phosphorus oxychloride promotes condensation and the product may be isolated as a hydrochloride.

***N*-Alkyldiaminomaleonitriles.** Di-(*tert*-octylamino)-maleonitrile has been prepared indirectly from reaction of diisobutene, hydrogen cyanide, and hydrogen fluoride.[10] *N*-Alkyldiaminomaleonitriles (alkyl group is ethyl, isopropyl, *tert*-butyl, and cyclohexyl) and *N,N'*-dialkyldiaminomaleonitriles (alkyl group is isopropyl and cyclohexyl) have been prepared in low yield from *N*-alkyliminoacetonitriles.[11] Di-(*tert*-butylamino)maleonitrile was obtained in low yield by oligomerization of *tert*-butyl isocyanide with hydrogen chloride followed by hydrolysis.[12]

DAMN can be converted indirectly to an *N*-alkyl derivative **2** by conversion to Schiff base **1** followed by reduction. *N*-Benzyldiaminomaleonitrile results from a benzaldehyde anil (**1**, R = C_6H_5) and *N*-alkyldiaminomaleonitriles are prepared from aliphatic aldehydes (R = cyclohexyl and *tert*-butyl). Schiff base **1** does not react with a second mole of aldehyde but *N*-benzyldiaminomaleonitrile (**2**, R = C_6H_5) forms Schiff base **3**, which can be reduced



to *N,N'*-dibenzyldiaminomaleonitrile (**4**). This new DAMN derivative was oxidized to dibenzyldiiminosuccinonitrile (**5**), which on standing isomerizes to **3** and an



isomer that also is reduced to **4**. Schiff base **3** has four possible isomeric forms about the imine and the carbon–carbon double bond. The structure of the intermediate **1** was established as the Schiff base rather than the isomeric dihydroimidazole by the presence of a low-field =CH proton in the nmr.

Direct tetramethylation of DAMN was accomplished by reaction of DAMN with excess sodium hydride at −30 to −20° to form the colorless monoanion followed by treatment with dimethyl sulfate at −10°. Nmr showed the