Chemistry of 2*H*-3,1-Benzoxazine-2,4(1*H*)-dione (Isatoic Anhydride). 2. Reactions with Thiopseudoureas and Carbanions

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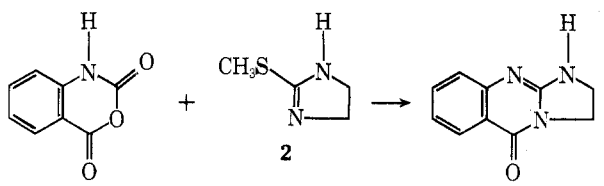
The reaction of 2*H*-3,1-benzoaxazine-2,4(1*H*)-diones with substituted thioureas leads to the formation of 2-aminoquinazolin-1*H*-4-ones. In the case of N-functionalized benzoxazines tricyclic systems are obtained. Carbanions derived from diethyl malonate and activated ethyl acetate derivatives produce substituted quinoline-2,4-diones on reaction with 2*H*-3,1-benzoxazine-2,4(1*H*)-diones.

During the past 30 years several groups have described the use of 2*H*-3,1-benzoxazine-2,4(1*H*)-dione (isatoic anhydride)[1] for the synthesis of quinazolinediones,[2] 4-quinazolinones,[3] pyrroloquinazolinones,[4] and 1,4-benzodiazepine-2,5-diones.[5] Most recently Ziegler[6] and our group[7,8] reported the utilization of isatoic anhydrides in the synthesis of fused quinazolinones, e.g., **3**.[8]

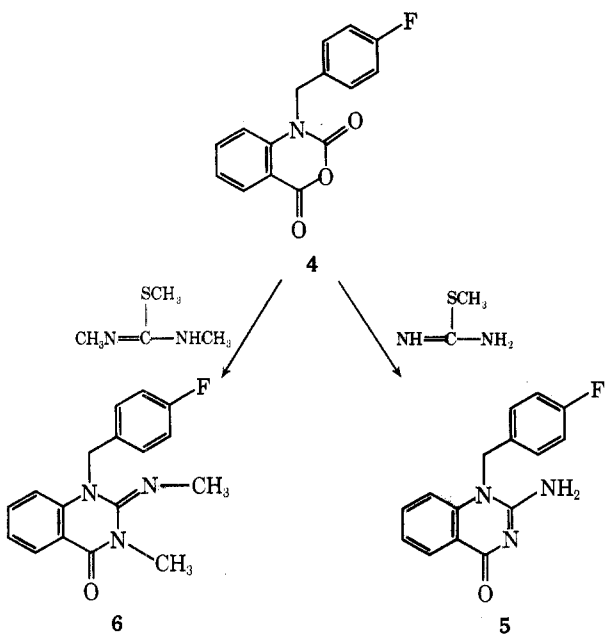


1 **2** **3**

In this publication we wish to report our investigations into the reactions of isatoic anhydrides with thiourea derivatives (Scheme I) and carbanions (Scheme III).

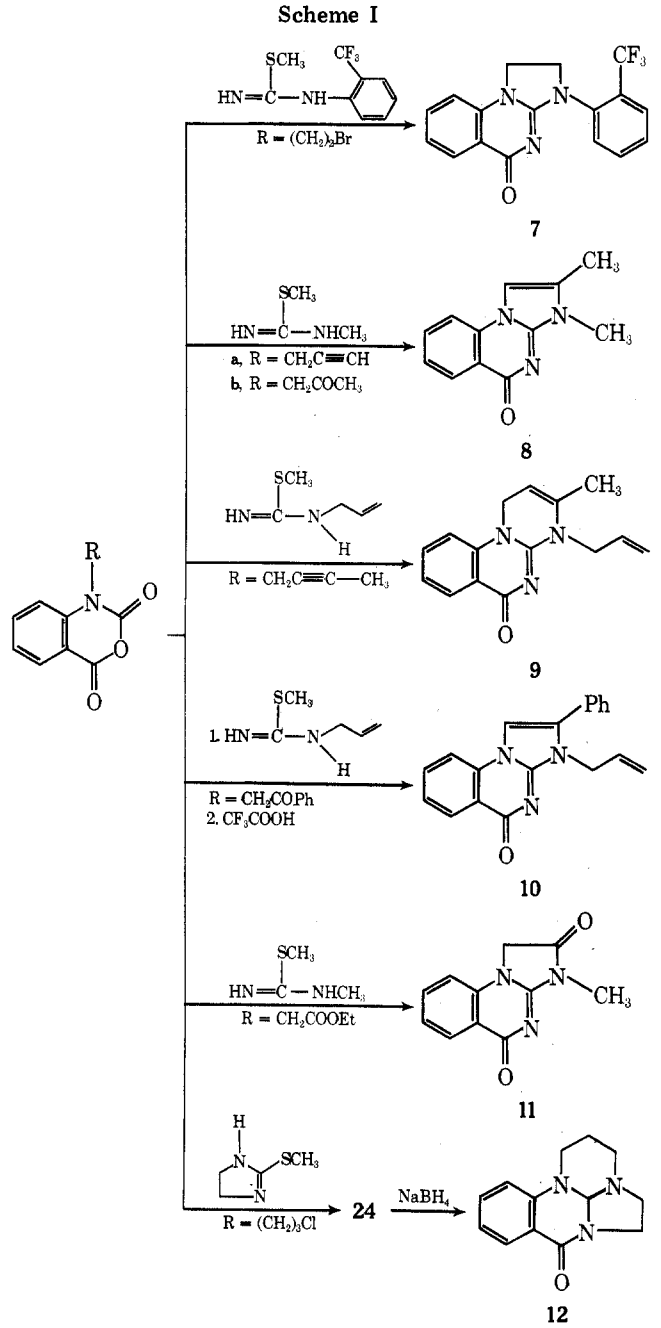
Discussion

Reactions with Thiopseudoureas. During our earlier work we had been concerned with the reaction of isatoic anhydrides with mono- and bicyclic thioureas. In this publication we wish to report some reactions of various isatoic anhydrides we have observed, including those bearing functional groups on the nitrogen atom, with thiopseudoureas (Scheme I). When symmetrically substituted thiopseudoureas are allowed to react with isatoic anhydrides (e.g., **4**) in refluxing dioxane the expected products (**5** or **6**) are isolated in satisfactory yields.



4 **6** **5**

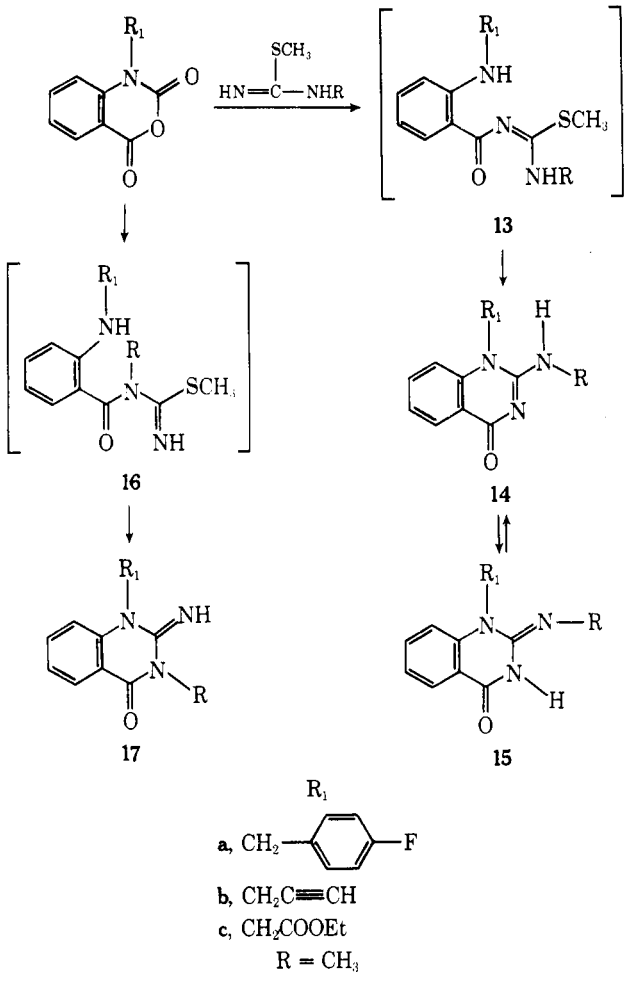
Scheme I



7 **8** **9** **10** **11** **12**

The question arises as to the course of the reaction when unsymmetrically substituted thiopseudoureas are employed (Scheme II). We assume that the initial step of the reaction involves a nucleophilic attack of one of the N atoms of the thiopseudourea onto the isatoic anhydride

Scheme II



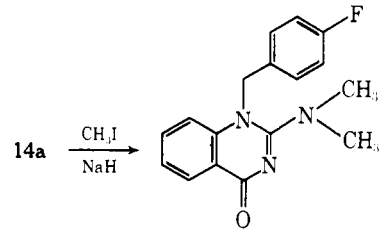
and that the first intermediate collapses, with concomitant loss of carbon dioxide, to yield **13** or **16**. Whether **13** or **16** is the product will depend on which of the N atoms (of the thiopseudourea) reacts with the anhydride. In the case of 2,3-dimethyl-2-thiopseudourea, N-3 might be the more basic nitrogen atom but would, on the other hand, be more sterically hindered during the inital step of the reaction. When 2,3-dialkyl-2-thiopseudoureas were allowed to react with isatoic anhydrides *one* final product **14** or **17** (Scheme II) was isolated. Considering the tautomeric forms in which compounds **14** may exist, interpretation of the NMR spectra did not permit a firm structure assignment. Our hope was therefore to be able to isolate the reaction intermediate **13** or **16** whose spectra might aid us in making an assignment as to the structure of the final product.

By the use of somewhat milder reaction conditions we were able to isolate the otherwise elusive intermediates (**13** or **16**) and fully characterize them in the cases where R_1 = $CH_2C{\equiv}CH$ (**13b**) and CH_2COOEt (**13c**), and R = CH_3. In the NMR spectra of both compounds the *N*-methyl group appeared as a doublet which collapsed to a singlet upon D_2O exchange. This finding strongly suggests that the isatoic anhydride is attacked by the less substituted nitrogen atom of the thiopseudourea and that **13** rather than **16** is the intermediate. It is interesting to note that the appearance of the *N*-methyl peak is also solvent dependent. The doublet is observed when $CDCl_3$ is used, but when the more polar solvent Me_2SO-d_6 is employed, only a singlet is seen. Subsequent cyclization of **13** yields compounds of the general structure **14** or **15**.

The question now arises as to the actual tautomeric form of these products. Upon comparison of the observed infrared carbonyl absorption frequencies with models where the C=N bond is unequivocally exocyclic to the quinazoline ring (namely **6**), it is found that the C=O absorption occurs at 1640 cm^{-1} accompanied by an additional band at 1680 cm^{-1} of almost equal intensity. This second band is assigned to stretching vibrations of the nonconjugated C=N group.[9]

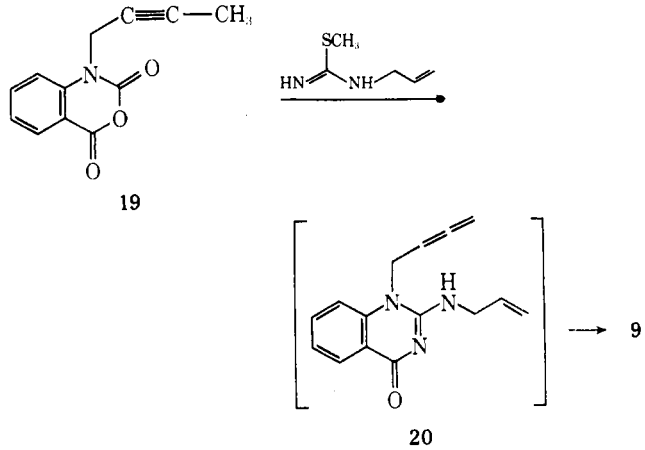
Compounds which do not have an exocyclic C=N bond (e.g., **18**) do not show this second band at 1680 cm^{-1}. We therefore conclude that the reaction products of 2,3-dialkyl-2-thiopseudoureas with isatoic anhydrides exist in the tautomeric structure **14**.

Compound **14a** can be alkylated with methyl iodide in the presence of sodium hydride to produce the *N,N*-dimethyl compound **18**.

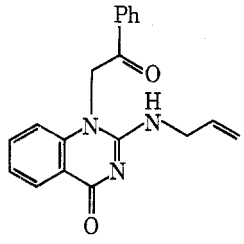


Alkylation occurs predominantly on the exocyclic nitrogen, but traces of **6**, formed by alkylation of the ring nitrogen, can be detected in the reaction mixture. As expected, in the NMR spectrum the methyl groups of **18** appear as a singlet whereas those of **6** appear as two distinct singlets. The infrared spectrum of **18** does not show the C=N band at 1680 cm^{-1}, which is in agreement with the conclusions drawn previously concerning product **14**.

In cases where the isatoic anhydride contains a highly reactive functional group on the nitrogen (e.g., 2-chloroethyl) no products of type **14** were isolated. Instead, concomitant reaction of the 2-amino function with the reactive group of the side chain leads to the formation of an additional ring (e.g., **7**). When *N*-(2-propynyl)isatoic anhydride (**27**) was allowed to react with 2,3-dimethyl-2-thiopseudourea in diglyme at reflux temperature, the product which was isolated lacked N–H absorption in its infrared spectrum and the characteristic features of the propynyl group. The appearance in the NMR spectrum of a *C*-methyl group at δ 2.3 and an olefinic proton at δ 7.5 strongly suggested structure **8**. Similar cyclizations of propynyl groups have been described and an allenic intermediate has been proposed.[10] Interestingly, the homologous isatoic anhydride **19** does not yield the corresponding ethyl analogue of **8**, but rather the six-membered derivative **9**. If indeed this cyclization proceeds through an allenic intermediate, the "terminal" allene **20** should be the precursor.

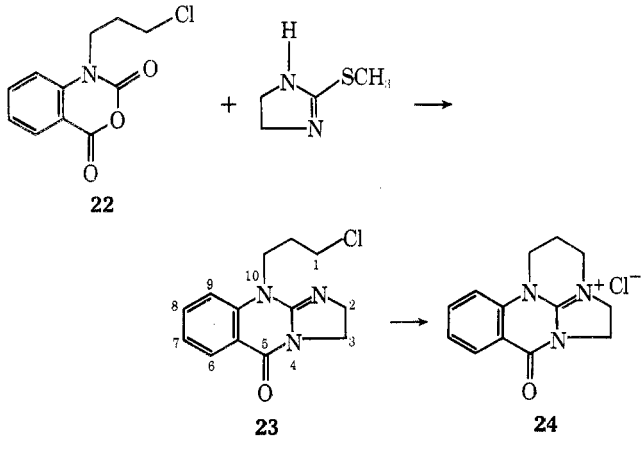


Not unexpectedly, the primary product of the reaction between a 3-allyl-2-methyl-2-thiopseudourea and *N*-phenacylisatoic anhydride was **21**. Treatment with trifluo-



21

roacetic acid transformed **21** into **10** (Scheme I). Having observed the ease of formation of the third ring in compounds such as **7**, we expected that a haloalkyl substituent in the side chain of the isatoic anhydride (e.g., **22**) could quaternize N-1 in the tricyclic intermediate **23** yielding the tetracyclic ammonium salt **24**. The isolation of **23** was not



22 **23** **24**

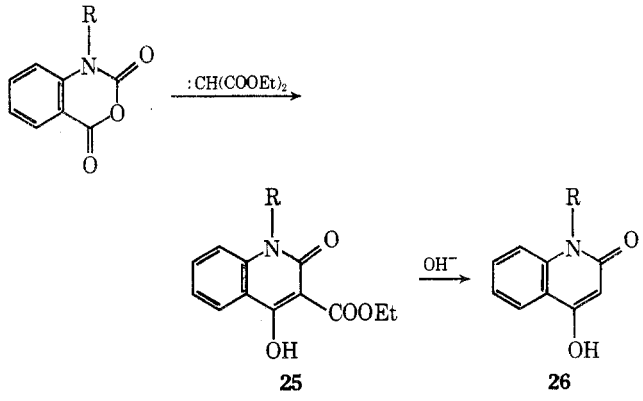
possible, **24** being formed directly. The crude **24** was reduced to **12** in moderate yield with sodium borohydride.

Reactions with Carbanions. To our knowledge the only reported reaction of 2*H*-3,1-benzoxazine-2,4(1*H*)-dione with a β-dicarbonyl compound is that with the anion of ethyl acetoacetate which leads to the formation of 3-carbethoxy-4-hydroxyquinaldine.[11] It was of interest to us to investigate the reactions of other carbanions with this substrate, particularly those of malonates, which should lead to the formation of quinoline-2,4-diones. These are otherwise only accessible through the acid-catalyzed reaction of malonic acid dianilids.[12] This standard method fails, however, in cases where the dianilids are substituted with strongly deactivating groups (e.g., NO_2). Also the *N*-alkylmalonic acid anilids are sometimes difficult to prepare, and reactive or acid-sensitive N substituents will not withstand the vigorous cyclization conditions. Furthermore, *N*-alkylquinoline-2,4-diones cannot be prepared by standard synthetic methods from quinoline-2,4-diones because alkylation occurs preferentially on oxygen, producing 4-alkoxyquinolin-2-ones (**41**, see Experimental Section).

In general we obtained the *N*-alkylquinolinediones (**26**) by allowing the sodium salt of diethyl malonate to react with the corresponding isatoic anhydrides at 120°C in dimethylacetamide followed by alkaline hydrolysis and decarboxylation of the ester group of **25**.

Since various *N*-alkylisatoic anhydrides are readily available[13] and the mildly basic reaction conditions do not interact with potentially reactive groups on the nitrogen, our synthesis avoids most of the difficulties inherent in the standard procedures.

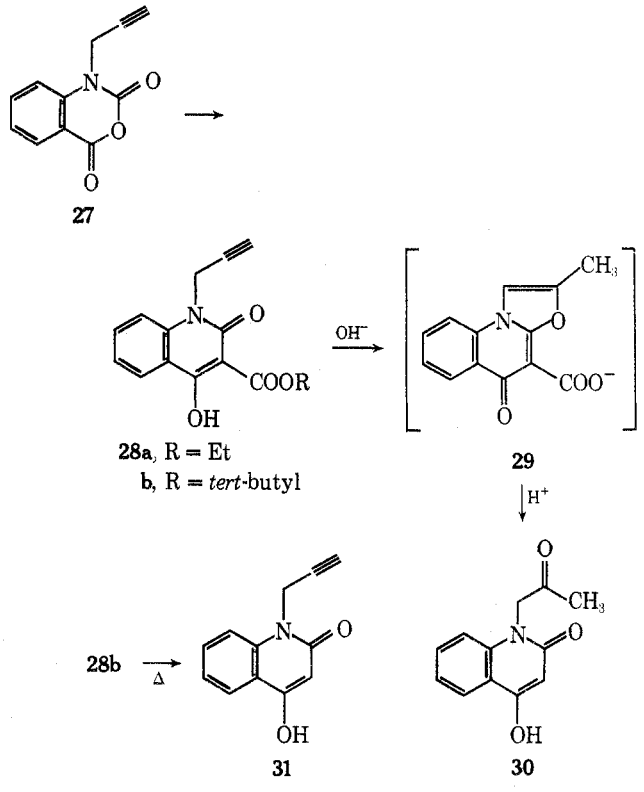
In the case of the *N*-propynyl derivative **28a**, concomi-



25 **26**

e.g. R = CH_3

tant hydration of the acetylenic bond occurred on hydrolysis, yielding **30** probably via the intermediate **29**. This reaction could be circumvented by use of di-*tert*-butyl malonate in the reaction with isatoic anhydride followed by the thermal decarboxylation of ester **28b**, thus giving the desired product **31**.



27

28a, R = Et
b, R = *tert*-butyl

29

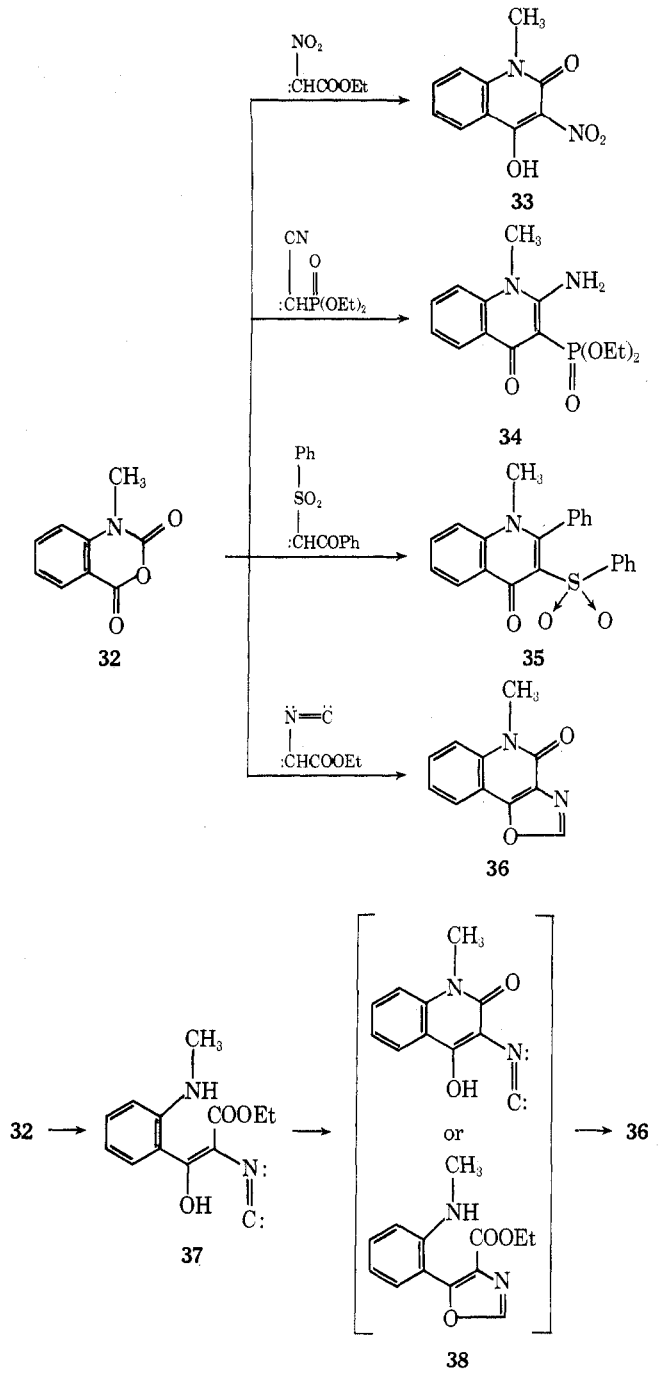
28b **31** **30**

The malonic esters can be replaced by various other compounds possessing an active methylene group and an electrophilic group capable of reacting with the liberated anilino nitrogen. The introduction of nitrogen, sulfur, and phosphorus substituents into the 3 position of the quinoline system can be accomplished by the reaction of isatoic anhydrides with the carbanion of the appropriate nitroacetate, phosphonoacetate, phosphonoacetonitrile, or β-ketosulfones (Scheme III).

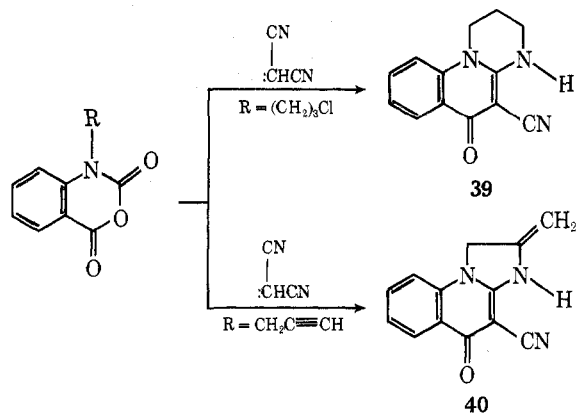
When **32** was treated with ethyl isocyanoacetate, the intermediate **37** spontaneously cyclized to yield **36** whose NMR spectrum ($CDCl_3$–Me_2SO-d_6) showed an olefinic proton at δ 8.4 besides the expected aromatic and methyl protons.

When the sodium salt of malononitrile was allowed to react with *N*-(3-chloropropyl)isatoic anhydride, the pyrimido[1,2-*a*]quinoline (**39**) was isolated (Scheme IV). Similarly, *N*-(2-propynyl)isatoic anhydride yielded the tricyclic

Scheme III



Scheme IV



product **40**. Contrary to our earlier observation (namely, the formation of **8**), the carbon–carbon double bond in the imidazole portion of this cyclization product was found to be exocyclic to the ring, as evident from the presence of a methylene group at δ 3.5 and two vinylic protons at δ 5.2 in the NMR spectrum.

Further investigations are presently being conducted into the formation of new heterocyclic ring systems using functionalized isatoic anhydrides.

Experimental Section[14]

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. NMR spectra were determined on Varian A-60 and T-60 spectrophotometers using Me_4Si as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).

Unless otherwise stated, all solutions of organic compounds were washed with brine and dried over Na_2SO_4. No attempt has been made to optimize the yields of the described reactions.

Procedure A (Preparation of Intermediates of Type 13). A suspension of 0.1 mol of the appropriate N-substituted isatoic anhydride, 0.1 mol of a 2,3-disubstituted 2-thiopseudourea hydriodide, and 11.7 g (0.11 mol) of Na_2CO_3 in 300 ml of CH_3CN was refluxed for 30 min. The solvent was removed under reduced pressure, and the residue suspended in 100 ml of CH_2Cl_2. The insoluble material was filtered off and washed twice with 50 ml of CH_2Cl_2. The solvent was exchanged for CH_3OH; and, upon cooling, crystallization occurred. The product was filtered, washed with Et_2O, and dried.

Procedure B (Cyclization of Intermediates of Type 13). A solution of 0.05 mol of intermediate **13** in 100 ml of diglyme was refluxed for 2 h (catalyzed by one pellet of NaOH). Upon cooling to room temperature, precipitation occurs. The resulting solid was filtered, washed with a small amount of EtOAc, and recrystallized from CH_2Cl_2 or CH_3OH.

Procedure C (Preparation of Quinazolin-4-ones from Substituted Isatoic Anhydrides). A suspension of 0.1 mol of the appropriate N-substituted isatoic anhydride, 0.1 mol of a 2,3-disubstituted 2-thiopseudourea hydriodide, and 11.7 g (0.11 mol) of Na_2CO_3 in 300 ml of CH_3CN was refluxed for 30 min. The solvent was removed under pressure, and the residue suspended in 100 ml of CH_2Cl_2. The insoluble salts were filtered off and washed twice with 50 ml of CH_2Cl_2. The CH_2Cl_2 was then replaced by 150 ml of diglyme and the reaction mixture (catalyzed by one pellet of NaOH) was heated under reflux for 2 h. Upon cooling to room temperature, precipitation occurs. The resulting solid was filtered, washed with a small amount of EtOAc, and recrystallized from CH_2Cl_2 or CH_3OH.

1-(*p*-Fluorobenzyl)-2-aminoquinazolin-1*H*-4-one (5). Using procedure C, 27.1 g (0.1 mol) of *N*-(*p*-fluorobenzyl)isatoic anhydride (**4**) and 21.8 g (0.1 mol) of 2-methyl-2-thiopseudourea hydriodide yielded 11.9 g of **5** (44%): mp 265–267°; ir (KBr) 3330, 3170, 1600 cm^{-1}; NMR (Me_2SO) δ 8.0 (m, 1), 7.3 (m, 9), 5.4 (s, 2).

Anal. Calcd for $C_{15}H_{12}N_3OF$: C, 66.9; H, 4.5; N, 15.6. Found: C, 67.0; H, 4.6; N, 15.4.

2,3-Dihydro-1-(*p*-fluorobenzyl)-3-methyl-2-methylimino-4-(1*H*)-quinazolinone (6). Using procedure C, 27.1 g (0.1 mol) of **4** and 24.6 g (0.1 mol) of 1,2,3-trimethyl-2-thiopseudourea hydriodide yielded 13.1 g of **6** (44%): mp 71–73°; ir ($CHCl_3$) 1640 cm^{-1}; NMR ($CDCl_3$) δ 8.1 (m, 1), 7.1 (m, 7), 5.2 (s, 2), 3.5 (s, 3), 3.3 (s, 3).

Anal. Calcd for $C_{17}H_{16}N_3OF$: C, 68.7; H, 5.4; N, 14.1. Found: C, 68.5; H, 5.5; N, 14.1.

2,3-Dihydro-3-(2-trifluoromethylphenyl)imidazo[1,2-*a*]-quinazolin-5(1*H*)-one (7). Using procedure C, 24.0 g of (2-bromoethyl)isatoic anhydride and 36.2 g of 3-(*o*-trifluoromethylphenyl)-2-methyl-2-thiopseudourea[15] yielded 8.6 g of **7** (free base) (26%): mp 222–224°; ir (KBr) 1605 cm^{-1}; NMR (Me_2SO) δ 7.6 (m, 8), 4.2 (m, 4).

Anal. Calcd for $C_{17}H_{12}N_3OF_3$: C, 61.6; H, 3.7; N, 12.7. Found: C, 61.5; H, 4.1; N, 12.9.

2,3-Dimethylimidazo[1,2-*a*]quinazolin-5(3*H*)-one (8). A. Using procedure B, **13b** yielded 5.3 g of **8** (49%): mp 237–240°; ir ($CHCl_3$) 1610 cm^{-1}; NMR (Me_2SO) δ 8.1 (m, 1), 7.8 (m, 3), 7.5 (m, 1), 3.4 (s, 3), 2.3 (d, 3).

Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.6; H, 5.2; N, 19.7. Found: C, 67.3; H, 5.2; N, 19.9.

B. Using procedure C, *N*-acetonylisatoic anhydride and 2,3-di-

methyl-2-thiopseudourea hydriodide yielded 5.8 g of **8** (27%). All physical constants and spectra were identical with those from the above route.

4-Allyl-3-methyl-1,4-dihydro-6*H*-pyrimido[1,2-*a*]quinazolin-6-one (9). Using procedure C, 21.5 g of *N*-(2-butynyl)isatoic anhydride and 25.8 g of 3-allyl-2-methyl-2-thiopseudourea hydriodide[16] yielded 5.1 g of **9** (20%): mp 131–135°; ir ($CDCl_3$) 1640 cm^{-1}; NMR (CF_3COOH) δ 8.0 (m, 5), 5.9 (m, 1), 5.5 (m, 2), 5.0 (d, 2), 4.4 (t, 2), 1.9 (s, 3).

Anal. Calcd for $C_{15}H_{15}N_3O$: C, 71.1; H, 6.0; N, 16.6. Found: C, 70.8; H, 6.3; N, 16.6.

3-Allyl-2-phenylimidazo[1,2-*a*]quinazolin-5(3*H*)-one (10). A solution of 6.4 g (0.02 mol) of **21** in 40 ml of CF_3COOH was stirred at room temperature for 30 min. The solution was evaporated to dryness and the residue was dissolved in 100 ml of 2 N aqueous NaOH. The solution was extracted three times with 50 ml of CH_2Cl_2 and the combined extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting solid was recrystallized from CH_2Cl_2–Et_2O to yield 5.4 g of **10** (89%): mp 198–200°, ir (KBr) 1595 cm^{-1}; NMR (CF_3COOH) δ 8.7 (m, 1), 8.1 (m, 4), 7.7 (s, 5), 6.0 (m, 1), 5.5 (d, 2), 5.0 (d, 2).

Anal. Calcd for $C_{19}H_{15}N_3O$: C, 75.7; H, 5.0; N, 14.0. Found: C, 75.9; H, 5.0; N, 13.7.

3-Methylimidazo[1,2-*a*]quinazoline-2,5(1*H*,3*H*)-dione (11). Using procedure B, **13c** yielded 6.2 g of **11** (28%): mp 285–288°; ir (KBr) 1620 cm^{-1}; NMR (CF_3COOH) δ 8.5–7.4 (m, 4), 5.2 (s, 2), 3.6 (s, 3).

Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.4; H, 4.2; N, 19.5. Found: C, 61.3; H, 4.4; N, 19.6.

2,3,4,4a-Tetrahydro-1*H*-4,5-ethanopyrimido[1,2-*a*]quinazolin-6-(5*H*)-one (12). A solution of 12 g (0.05 mol) of **22**, 5.8 g (0.05 mol) of 2-methylthio-2-imidazoline, and a catalytic amount of KOH in 250 ml of dioxane was refluxed for 2.5 h. Upon cooling to room temperature the resulting precipitate (**24**) was filtered, washed with Et_2O, and dissolved in 200 ml of 50% aqueous EtOH. This was then added to a solution of 2.4 g of sodium borohydride in 40 ml of 80% EtOH at −15° and the mixture was stirred at −10° for 30 min. After 200 ml of cold H_2O was added to the mixture, the solvent was concentrated to 50 ml under reduced pressure. The resulting precipitate was filtered, washed with H_2O, and recrystallized from CH_2Cl_2–Et_2O to yield 3.7 g of **12** (32%): mp 144–146°; ir ($CHCl_3$) 1645 cm^{-1}; NMR ($CDCl_3$) δ 7.9 (m, 1), 7.0 (m, 3), 4.5 (s, 1), 4.1–1.5 (m, 10).

Anal. Calcd for $C_{13}H_{15}N_3O$: C, 68.1; H, 6.6; N, 18.3. Found: C, 68.3; H, 6.6; H, 18.6.

1-[2-(*p*-Fluorobenzylamino)benzoyl]-2,3-dimethyl-2-thiopseudourea (13a). Using procedure A, 27.3 g of **4** and 23.2 g of 2,3-dimethyl-2-thiopseudourea hydriodide yielded 23.6 g of **13a** (73%): mp 101–102°, ir ($CHCl_3$) 3320, 1620 cm^{-1}; NMR ($CDCl_3$) δ 8.1 (m, 1), 8.4 (m, 1), 6.9 (m, 7), 4.4 (d, 2), 3.0 (d, 3) 2.4 (s, 3).

Anal. Calcd for $C_{17}H_{18}N_3OSF$: C, 60.2; H, 5.7; N, 13.2; S, 10.0. Found: C, 60.1; H, 5.8; N, 12.8; S, 9.9.

1-[2-(2-Propynylamino)benzoyl]-2,3-dimethyl-2-thiopseudourea (13b). Using procedure A, 20.1 g of *N*-(2-propynyl)isatoic anhydride (**27**) and 23.2 g of 2,3-dimethyl-2-thiopseudourea hydriodide yielded 23.9 g of **13b** (91%): mp 93–96°, ir ($CHCl_3$) 3300, 1615 cm^{-1}; NMR ($CDCl_3$) δ 8.7 (t, 1), 8.1 (m, 1), 7.3 (m, 1), 6.7 (m, 2), 4.0 (q, 2), 3.3 (m, 1), 3.0 (m, 4), 2.4 (s, 3).

Anal. Calcd for $C_{13}H_{15}N_3OS$: C, 59.7; H, 5.8; N, 16.1; S, 12.3. Found: C, 59.8; H, 5.7; N, 15.7; S, 11.9.

1-[2-(Ethoxycarbonylmethylamino)benzoyl]-2,3-dimethyl-2-thiopseudourea (13c). Using procedure B, 24.9 g of *N*-ethoxycarbonylmethylisatoic anhydride and 23.2 g of 2,3-dimethyl-2-thiopseudourea hydriodide yielded 28.7 g of **13c** (93%): mp 67–70°; ir ($CHCl_3$) 1750, 1620 cm^{-1}; NMR ($CDCl_3$) δ 10.8 (m, 1), 9.0 (m, 1), 8.3 (m, 1), 7.3 (m, 1), 6.5 (m, 2), 4.2 (m, 4), 3.0 (d, 3), 2.5 (s, 3), 1.2 (t, 3).

Anal. Calcd for $C_{14}H_{19}N_3O_3S$: C, 54.3; H, 6.1; N, 13.6; S, 10.4. Found: C, 54.3; H, 6.5; N, 14.1; S, 10.9.

1-(*p*-Fluorobenzyl)-2-methylaminoquinazolin-1*H*-4-one (14a). Using procedure B, **13a** yielded 11.1 g of **14a** (74%): mp 253–256°; ir (KBr) 3250, 1600 cm^{-1}; NMR (Me_2SO) δ 8.1 (m, 1), 7.3 (m, 8), 5.4 (s, 2), 2.9 (d, 3).

Anal. Calcd for $C_{16}H_{14}N_3OF$: C, 67.8; H, 5.0; N, 14.8. Found: C, 67.6; H, 5.2; N, 14.7.

1-(*p*-Fluorobenzyl)-2-dimethylaminoquinazolin-1*H*-4-one (18). To a suspension of 0.4 g of NaH (57%, pentane washed) in 30 ml of dimethylacetamide was added 2.83 g (0.01 mol) of **14a** in portions. After the evolution of hydrogen ceased 1.55 g (0.011 mol) of CH_3I was added and the mixture was stirred at room temperature for 3 days. The reaction mixture was poured onto ice–water and the resulting precipitate was filtered off (this was found to be mostly **6**). The aqueous phase was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated and upon the addition of Et_2O furnished 1.15 g of **18** (38%): mp 166–170°; ir ($CHCl_3$) 1645 cm^{-1}; NMR ($CDCl_3$–Me_2SO) δ 8.0 (m, 1), 7.1 (m, 7), 5.25 (s, 2), 3.0 (s, 6).

Anal. Calcd for $C_{17}H_{16}N_3OF$: C, 68.7; H, 5.4; N, 14.1. Found: C, 68.8; H, 5.6; N, 14.2.

2-Allylamino-1-phenacylquinazolin-4(1*H*)-one (21). Using procedure C, *N*-phenacylisatoic anhydride and 3-allyl-2-methyl-2-thiopseudourea hydriodide yielded 16.6 g of **21** (52%): mp 245° dec; ir (KBr) 3060, 1610 cm^{-1}.

Anal. Calcd for $C_{19}H_{17}N_3O_2$: C, 71.4; H, 5.4; N, 13.2. Found: C, 71.4; H, 5.2; N, 13.0.

1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylic Acid Ethyl Ester (25). To a solution of 21.0 g (0.13 mol) of diethyl malonate in 75 ml of dimethylacetamide was added 5.3 g (0.13 mol) of NaH (57%, pentane washed) in portions. When the evolution of hydrogen ceased, the solution was stirred for 15 min and was placed in an oil bath at 80°. To this a solution of 22.0 g (0.125 mol) of **32** in 125 ml of dimethylacetamide was added dropwise over a period of 15 min (CO_2 evolution occurs). The mixture was stirred at 120° for 18 h. The resulting precipitate was filtered, washed twice with Et_2O, and then dissolved in 600 ml of warm H_2O. After treatment with charcoal, the solution was acidified with 6 N HCl and the precipitate was filtered, washed with water, and crystallized from CH_2Cl_2–Et_2O to yield 20.5 g of **25** (67%): mp 100–102°; ir ($CHCl_3$) 1650, 1625 cm^{-1}; NMR ($CDCl_3$) δ 12.9 (s, 1), 8.1 (m, 1), 7.8–7.1 (m, 3), 4.5 (q, 2), 3.6 (s, 3), 1.5 (t, 3).

Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.2; H, 5.3; N, 5.7. Found: C, 63.2; H, 5.6; N, 5.4.

4-Hydroxy-1-methyl-2(1*H*)-quinolinone (26). A mixture of 2.0 g (0.008 mol) of **25** in 40 ml of 2 N aqueous NaOH was refluxed for 3 h. The resulting solution was cooled and acidified with 6 N HCl. Precipitation and CO_2 evolution occurred. The precipitate was filtered, washed well with water, and dried in vacuo to yield 1.2 g of **26** (86%), mp 266–270° (lit.[12] mp 265°).

1,2-Dihydro-4-hydroxy-1-(2-propynyl)-2-oxo-3-quinolinecarboxylic Acid Ethyl Ester (28a). Using the procedure for **25**, but a reaction time of 4 h, 8.0 g (0.04 mol) of **27** and 6.5 g (0.04 mol) of diethyl malonate yielded 7.8 g of **28a** (70%): mp 171–174°; ir ($CHCl_3$) 3330, 1665, 1635 cm^{-1}; NMR ($CDCl_3$) δ 14.4 (s, 1), 8.25 (m, 1), 7.5 (m, 3), 5.1 (d, 2), 4.5 (q, 2), 2.25 (t, 1), 1.5 (t, 3).

Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.4; H, 4.8; N, 5.2. Found: C, 66.3; H, 5.0; N, 4.8.

1,2-Dihydro-4-hydroxy-1-(2-propynyl)-2-oxo-3-quinolinecarboxylic Acid *tert*-Butyl Ester (28b). Using the procedure for **25** but a reaction time of 5 h, 21.0 g (0.105 mol) of **27** and 25.0 g (0.115 mol) of di-*tert*-butyl malonate yielded 18.0 g of **28b** (57%): mp 168–170°; ir ($CHCl_3$) 3300, 1650, 1620 cm^{-1}; NMR ($CDCl_3$) δ 14.6 (s, 1), 8.25 (m, 1), 7.5 (m, 3), 5.05 (d, 2), 2.25 (t, 1), 1.7 (s, 9).

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.2; H, 5.7; N, 4.7. Found: C, 68.0; H, 5.9; N, 4.6.

1-Acetonyl-4-hydroxy-2(1*H*)-quinolinone (30). A mixture of 7.7 g of **28a** in 125 ml of 2 N NaOH was refluxed for 90 min. The resulting solution was cooled and acidified with 6 N HCl (precipitation and CO_2 evolution occurred). The precipitate was filtered, washed well with water, and dried in vacuo to yield 5.5 g of **30** (90%): mp 257–260°; ir (Nujol) 1720, 1640 cm^{-1}; NMR (Me_2SO) δ 11.6 (s, broad, 1), 8.0 (m, 1), 7.4 (m, 3), 5.95 (s, 1), 5.2 (s, 2), 2.25 (s, 3).

Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.4; H, 5.1; N, 6.4. Found: C, 66.0; H, 4.8; N, 6.3.

4-Hydroxy-1(2-propynyl)-2(1*H*)-quinolinone (31). A suspension of 5.0 g of **28b** in 85 ml of *o*-dichlorobenzene was heated slowly from 100 to 170° (a solution forms) and was kept at 170° for 2 h (when the temperature reached 170° gas evolution begins and a precipitate forms). The reaction mixture was cooled and the precipitate was filtered, washed with Et_2O, and recrystallized from MeOH to yield 3.0 g of **31** (90%): mp 211–214°; ir (Nujol) 3290, 1650 cm^{-1}; NMR (Me_2SO) δ 11.1 (s, broad, 1), 8.0 (m, 1), 7.5 (m, 3), 5.9 (s, 1), 5.1 (d, 2), 3.2 (t, 1).

Anal. Calcd for $C_{12}H_9NO_2$: C, 72.4; H, 4.5; N, 7.0. Found: C, 72.0; H, 4.8; N, 6.7.

4-Hydroxy-1-methyl-3-nitro-2(1*H*)-quinolinone (33). The reaction was carried out similarly to that of compound **25**. The solvent from the reaction mixture was removed under reduced pressure, and the residue was dissolved in H_2O. After acidification with 6 N HCl the resulting precipitate was filtered, washed with water,

and recrystallized from CH_2Cl_2–Et_2O to yield **33** (42%): mp 169–170°; ir ($CHCl_3$) 1670, 1630, 1540, 1430 cm^{-1}; NMR ($CDCl_3$–Me_2SO) δ 11.3 (s, broad, 1), 8.1 (m, 1), 7.9–7.1 (m, 3), 3.65 (s, 3).

Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.6; H, 3.7; N, 12.7. Found: C, 54.3; H, 3.9; N, 12.4.

(2-Amino-1,4-dihydro-1-methyl-4-oxoquinolin-3-yl)phosphonic Acid Diethyl Ester (34). To a solution of 8.8 g (0.05 mol) of diethyl cyanomethylphosphonate in 75 ml of dimethylacetamide, 2.1 g (0.05 mol) of NaH (57%, pentane washed) was added in portions. When the evolution of hydrogen ceased, the solution was stirred for 15 min. A solution of 8.8 g (0.05 mol) of **32** in 75 ml of dimethylacetamide was then added. The resulting mixture was placed in an oil bath, and the temperature was raised slowly to 120° and kept there for 4 h (CO_2 evolution occurs). The solvent was removed under reduced pressure, and water was added to the residue. The mixture was extracted into EtOAc, washed with brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to produce 15 g of an oil which was readily crystallized from Et_2O to yield 11.4 g of **34** (74%): mp 193–196°; ir ($CHCl_3$) 3490, 3300, 3140, 1620, 1570, 1510 cm^{-1}; NMR ($CDCl_3$) δ 8.3 (m, 1), 8.1 (s, 2), 7.8–7.1 (m, 3), 4.2 (m, 4), 3.8 (s, 3), 1.3 (t, 6).

Anal. Calcd for $C_{14}H_{19}N_2O_4P$: C, 54.2; H, 6.2; N, 9.0. Found: C, 53.8; H, 6.2; N, 9.0.

1-Methyl-2-phenyl-3-phenylsulfonylquinolin-4(1*H*)-one (35). To a solution of 10.0 g (0.038 mol) of phenyl phenacylsulfone in 100 ml of dimethylacetamide, 1.85 g (0.038 mol) of NaH (50%, pentane washed) was added in portions. When the evolution of hydrogen ceased, the solution was stirred for 15 min and placed in an oil bath at 120°. To this, a solution of 6.8 g (0.038 mol) of **32** in 50 ml of dimethylacetamide was added dropwise over a period of 10 min (CO_2 evolution occurs). The mixture was stirred at 120° for 18 h. The solvent was removed under reduced pressure, and water was added to the residue. The resulting precipitate was washed twice with water and recrystallized from CH_2Cl_2–Et_2O to yield 5.2 g of **35** (36%): mp 268–270°; ir ($CHCl_3$) 1620, 1600, 1390, 1160, 1145 cm^{-1}; NMR ($CDCl_3$–Me_2SO) δ 8.3 (m, 1), 8.0–7.3 (m, 13), 3.4 (s, 3).

Anal. Calcd for $C_{22}H_{17}NO_3S$: C, 70.4; H, 4.6; N, 3.7; S, 8.5. Found: C, 70.0; H, 4.8; N, 3.6; S, 8.5.

5-Methyloxazolo[4,5-*c*]quinolin-4(5*H*)-one (36). To a solution of 5.7 g (0.05 mol) of ethyl isocyanoacetate[17] in 75 ml of dimethylacetamide, 2.1 g (0.05 mol) of NaH (57%, pentane washed) was added in portions. When the evolution of hydrogen ceased, the solution was stirred for 15 min. A solution of 8.8 g (0.05 mol) of **32** in 75 ml of dimethylacetamide was then added. The resulting mixture was placed in an oil bath. The temperature was raised slowly to 120° and kept there for 5 h (CO_2 evolution occurs). The solvent was removed under reduced pressure, and H_2O was added to the residue. The resulting precipitate was filtered, washed well with H_2O, and crystallized from CH_2Cl_2–Et_2O to yield 2.6 g of **36** (45%): mp 191–194°; ir ($CHCl_3$) 1670, 1585 cm^{-1}; NMR ($CDCl_3$–Me_2SO) δ 8.4 (s, 1) 8.0–7.2 (m, 4), 3.8 (s, 3).

Anal. Calcd for $C_{11}H_8N_2O_2$, C, 66.0; H, 4.0; N, 14.0. Found: C, 66.1; H, 4.0; N, 14.1.

5-Cyclopropylmethyloxazolo[4,5-*c*]quinolin-4(5*H*)-one. Using the procedure for that of compound **36**, *N*-cyclopropylmethylisatoic anhydride[13] and ethyl isocyanoacetate yielded 38% of product, mp 164–167°.

Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 70.0; H, 5.0; N, 11.7. Found: C, 69.6; H, 5.3; N, 11.6.

8-Chloro-5-methyloxazolo[4,5-*c*]quinolin-4(5*H*)-one. Using the procedure for that of compound **36**, 6-chloro-1-methyl-2*H*-3,1-benzoxazine-2,4(1*H*)-dione and ethyl isocyanoacetate yielded 33% of product mp 210–213°.

Anal. Calcd for $C_{11}H_7N_2O_2Cl$: C, 56.3; H, 3.0; N, 11.9; Cl, 15.1. Found: C, 55.9; H, 3.3; H, 11.7; Cl, 15.2.

5-Methyl-7,8-methylenedioxyoxazolo[4,5-*c*]quinolin-4(5*H*)-one. Using the procedure for that of compound **36**, 1-methyl-6,7-methylenedioxy-2*H*-3,1-benzoxazine-2,4(1*H*)-dione[13] and ethyl isocyanoacetate yielded 35% product, mp >310°.

Anal. Calcd for $C_{12}H_8N_2O_4$: C, 59.0; H, 3.3; N, 11.5. Found: C, 58.8; H, 3.5; N, 11.4.

2,3,4,6-Tetrahydro-6-oxo-1*H*-pyrimido[1,2-*a*]quinoline-5-carbonitrile (39). To a solution of 1.4 g (0.021 mol) of malononitrile in 20 ml of dimethylacetamide, 0.9 g (0.021 mol) of NaH (57%, pentane washed) was added in portions. When the evolution of hydrogen ceased, the solution was stirred for 15 min. A solution of 5.0 g (0.021 mol) of **22**[13] in 45 ml of dimethylacetamide was then added dropwise over a period of 30 min. The mixture was stirred at room temperature for 30 min, then at 120° for 18 hr (CO_2 evolution occurs). The mixture was then poured on H_2O. The resulting precipitate was filtered and washed with H_2O, MeOH, and Et_2O to yield 2.7 g of **39** (58%). A sample was crystallized from EtOAc: mp 267–269°; ir (Nujol) 3300, 2200, 1600, 1550, 1460 cm^{-1}; NMR (Me_2SO) δ 8.15 (m, 1), 7.8–7.2 (m, 4), 4.3 (m, 2), 3.85 (t, 2), 2.2 (m, 2).

Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.3; H, 4.9; N, 18.7. Found: C, 69.0; H, 5.1; N, 18.8.

1,2,3,5-Tetrahydro-2-methylene-5-oxoimidazo[1,2-*a*]quinoline-4-carbonitrile (40). To a solution of 1.7 g (0.026 mol) of malononitrile in 20 ml of dimethylacetamide was added 1.1 g (0.026 mol) of NaH (57%, pentane washed) in portions. When the evolution of hydrogen ceased, a solution of 5.0 g (0.025 mol) of **27**[13] in 30 ml of dimethylacetamide was added dropwise over a period of 5 min. The mixture was stirred at room temperature for 15 min and then at 120° for 2 h. The reaction mixture was concentrated to one-fourth volume and was poured onto 100 ml of cold H_2O. The solution was acidified with 2 N HCl and the resulting precipitate was filtered, washed with H_2O, and triturated with hot EtOH to yield 4.5 g of **40** (82%): mp 285° (then resolidifies); ir (Nujol) 3340, 3200, 2210, 1680 cm^{-1}; NMR (Me_2SO) δ 8.2 (m, 1), 8.0–7.3 (m, 4), 5.2 (d, 2), 3.5 (s, 2).

Anal. Calcd for $C_{13}H_9N_3O$: C, 69.9; H, 4.1; N, 18.8. Found: C, 70.2; H, 4.0; N, 18.5.

4-Ethoxy-2(1*H*)-quinolinone (41). To a suspension of 6.0 g of 2,4-quinolinediol in 50 ml of dimethylacetamide was added 1.6 g of NaH (57%, pentane washed) in portions. When the evolution of hydrogen ceased, 6.0 g of ethyl iodide was added. The mixture was stirred at 30–35° for 5 min and then at room temperature for 18 h. The resulting precipitate was filtered and crystallized from MeOH to yield 2.8 g of **41** (40%): mp 223–226°; ir (Nujol) 1640 cm^{-1}; NMR (Me_2SO) δ 11.6 (s, broad, 1), 7.5 (m, 4), 6.0 (s, 1), 4.3 (q, 2), 1.5 (t, 3).

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.8; H, 5.9; N, 7.4. Found: C, 69.9; H, 5.5; N, 7.3.

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References and Notes

(1) Throughout this paper the names "isatoic anhydride" and "2*H*-3,1-benzoxazine-2,4(1*H*)-dione" are used interchangeably. Commercial sources still prefer the first name whereas *Chemical Abstracts* subscribes to the latter. We have adopted the *Chemical Abstracts* numbering system for substituted isatoic anhydrides, but we feel that it will be easier to read if we use the expression "N-substituted isatoic anhydride" rather than "N-substituted 2*H*-3,1-benzoxazine-2,4(1*H*)-dione".
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Thermal Decomposition of 2*H*-Azirines. Formation of Products Resulting from Carbon–Carbon Bond Cleavage[1]

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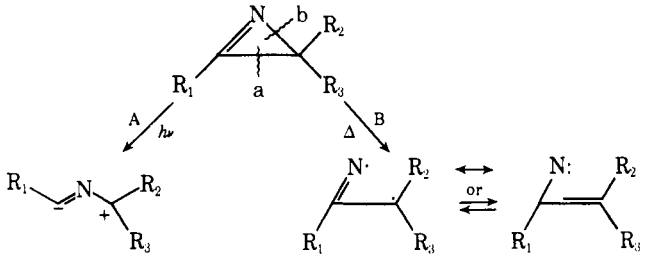
The synthesis and thermal decomposition of 2-methyl-3-phenyl- (**19a**), 2-ethyl-3-phenyl- (**19b**), 2,2-dimethyl-3-phenyl- (**19c**), and 2,3-dimethyl-2-phenyl-2*H*-azirines (**19d**) is described. Previously, products formed on thermal decomposition of 2*H*-azirines have been derived from initial C–N bond cleavage; in contrast, the products observed on heating **19a–c** (styrenes, benzonitrile, and HCN or acetonitrile) are formed by C–C cleavage, leading initially to iminocarbene intermediates. Evidence is presented that the primary mode of product formation from such an intermediate is 1,4-hydrogen shift, giving a 2-azabutadiene. The azabutadiene then fragments (via a small equilibrium concentration of substituted 1-azacyclobutene) leading to the final products. At higher temperatures, the azabutadienes are converted to dihydroisoquinolines as well.

Photochemical and thermal bond cleavage preferences in 2*H*-azirines appear to be quite distinct. Products formed during photochemical isomerizations appear to always involve carbon–carbon bond cleavage (path A, Scheme I), while thermal isomerization products arise from initial carbon–nitrogen bond cleavage (path B, Scheme I).

Scheme I



Azirine photochemistry has been extensively investigated by several groups. Padwa[3] and Schmid,[4] for example, have shown in independent studies that upon photolysis 3-phenyl-2*H*-azirines undergo cycloadditions with a variety of 1,3-dipolarophiles. These reactions apparently all proceed by initial C–C cleavage in the azirines, leading to dipolar species. Schmid and co-workers have also photolyzed triphenyl-2*H*-azirine in a 2,2-dimethylbutane–pentane matrix at −185 °C and observed a new uv maximum at ca. 350 nm ($\epsilon \sim 10^4$). The authors assigned this band to a nitrile ylide species. They further showed that the ylide rearranged to starting azirine only photochemically, and were able to trap it at low temperatures using methyl trifluroacetate. Recent ab initio MO calculations by Salem,[5] utilizing a configuration interaction treatment, suggest that upon cleaving a C–C azirine bond, the ground state nitrile ylide energy surface is best reached by internal conversion from a singlet n,π* state at a C–N–C bond angle of 100°. Salem's calculations also predict a large barrier for thermal conversion of the ylide to azirine, but suggest a facile photochemical conversion.

Relative to the well-defined photochemistry of 2*H*-azirines, their thermal behavior is not as well understood. The first report of a 2*H*-azirine pyrolysis was made by Isomura and co-workers in 1968.[6] These workers prepared 2-phenyl-2*H*-azirine (**1**) and 3-methyl-2-phenyl-2*H*-azirine (**2**) by photolytic and thermal decomposition of *cis*- and *trans*-1-azido-2-phenylethene (**3c** and **3t**) and *cis*- and *trans*-2-azido-1-phenylpropene (**4c** and **4t**), respectively. Thermal decomposition of **1** in boiling hexadecane yielded a 1:1 mixture of indole (**5**) and phenylacetonitrile (**6**) in 86% isolated yield. Similar treatment of **2** gave only 2-methylindole (**7**). The most obvious mechanism for formation of **5**, **6**, and **7** involved a vinyl nitrene intermediate generated by rupture of the *carbon–nitrogen* bond, followed by insertion into the phenyl group or α-carbon–hydrogen bond (see Scheme II).

Scheme II