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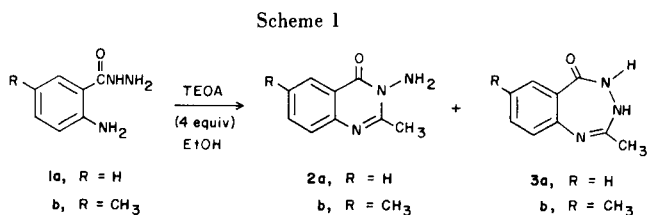
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The cyclization of *o*-aminobenzoylhydrazine (**1a**) and its 5-methyl derivative **1b** with four equivalents and with one equivalent of triethyl orthoacetate (TEOA) was studied. 3-Amino-2-methyl-4(3*H*)-quinazolinone (**2a**), 3,4-dihydro-2-methyl-5*H*-1,3,4-benzotriazepin-5-one (**3a**) and an imino ether derivative of **2a**, *N*-[2-methyl-4-oxo-3(4*H*)-quinazolinyl]ethanimidic acid ethyl ester (**4a**) were obtained from the reaction of **1a** with four equivalents of TEOA. These results were compared with those of Merour [1] who isolated **2a** and **3a** using the same conditions. When **1a** was treated with one equivalent of TEOA, **2a**, **3a**, and a new product, 2-(5-methyl-1,3,4-oxadiazol-2-yl)benzenamine (**5a**) were produced, and **4a** was not. Similar results were obtained with the reactions of **1b** with TEOA. Authentic samples of oxadiazoles **5a** and **b** were prepared by alternate routes. Novel acid-catalyzed rearrangements of benzotriazepinones **3a** and **b**, to mixtures of aminoquinazolinones **2a** and **b** and oxadiazoles **5a** and **b**, respectively, were found. The different relative amounts of aminoquinazolinones **2** and oxadiazoles **5** which were produced from these rearrangements allowed us to choose between two potential mechanisms for these interesting rearrangements. Treatment of 5-nitrobenzoylhydrazine (**37**) with four equivalents of TEOA gave three products which were characterized, but did not lead to benzotriazepinone formation.

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A recent report by Merour [1] describes the conversion of *o*-aminobenzoylhydrazine (**1a**) to 3-amino-2-methyl-4(3*H*)-quinazolinone (**2a**) and 3,4-dihydro-2-methyl-5*H*-1,3,4-benzotriazepin-5-one (**3a**) on treatment with four equivalents of triethyl orthoacetate (TEOA) in ethanol. Likewise, the 5-methyl derivative of **1a**, **1b**, was converted to quinazolinone **2b** and benzotriazepinone **3b**. The products of these reactions were separated by fractional crystallization, and the yields and reported physical constants are displayed in Scheme 1.



Compound	Results of Merour [1] Yield (%)	Mp (°C)
2a	15	145
2b	11	170
3a	40	205
3b	20	200

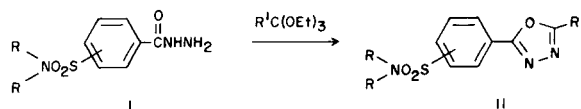
We thought it was curious that oxadiazoles were not reported products of these reactions, since the cyclization of arylhydrazides with orthoformic esters comprises a standard method for the synthesis of 2-aryl-1,3,4-oxadiazoles [2-4]. We have demonstrated in our laboratories that 2,5-

disubstituted oxadiazoles are readily produced from arylhydrazides and higher ortho esters, namely, triethyl orthoacetate, triethyl orthopropionate and triethyl orthobenzoate. Table 1 lists a series of oxadiazoles which were prepared in high yield from [(dialkylamino)sulfonyl]benzoic acid hydrazides and these ortho esters (as well as triethyl orthoformate), as potential antiviral agents. Thus, it seemed unusual that oxadiazoles were not reported [1] as products resulting from treatment of arylhydrazides **1a** and **b** with TEOA.

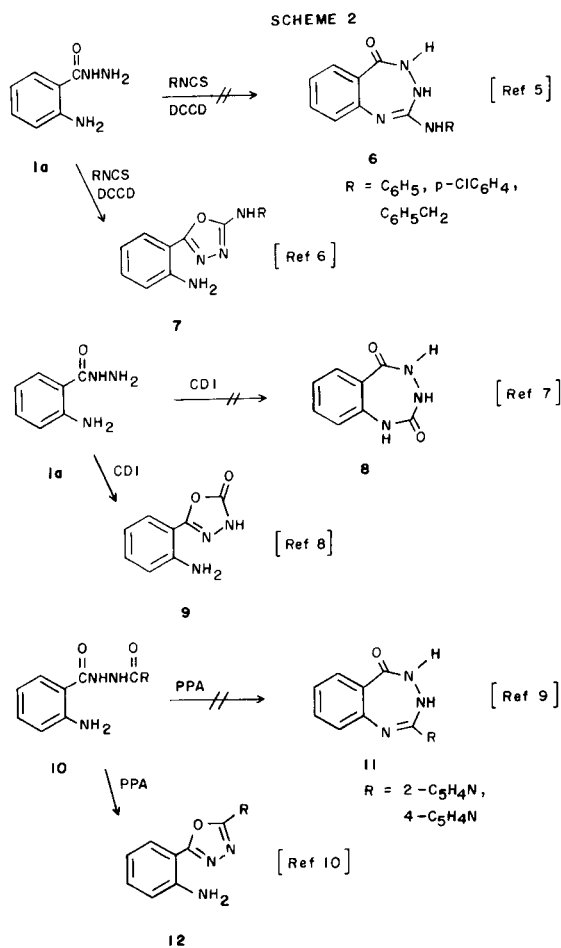
In addition, recent reports have shown that oxadiazoles rather than benzotriazepines were produced when monoacid hydrazides were treated with reagents which introduced one-carbon fragments, and when di-acid hydrazides underwent dehydrative cyclization (Scheme 2). Treatment of anthranilhydrazide (**1**) with isothiocyanates (RNCS) and *N,N'*-dicyclohexylcarbodiimide (DCCD) reportedly gave benzotriazepinones **6** [5], but a reinvestigation [6] of this work showed the products to be the oxadiazoles **7**, instead. Likewise, insertion of a one-carbon (carbonyl) fragment into **1a** using 1,1'-carbonyldiimidazole (CDI) did not produce benzotriazepinedione **8** as initially reported [7], but oxadiazolone **9**, instead [8]. Also, a correction in the assignment of compounds resulting from polyphosphoric acid (PPA) cyclodehydration of diacylhydrazines **10** has been reported [10]. These compounds are oxadiazoles **12** [10] rather than benzotriazepinones **11** [9].

In Scheme 3 are shown the results of the present study on the reaction of *o*-aminobenzoylhydrazine (**1a**) and its 5-methyl analog **2b** with triethyl orthoacetate (TEOA). The

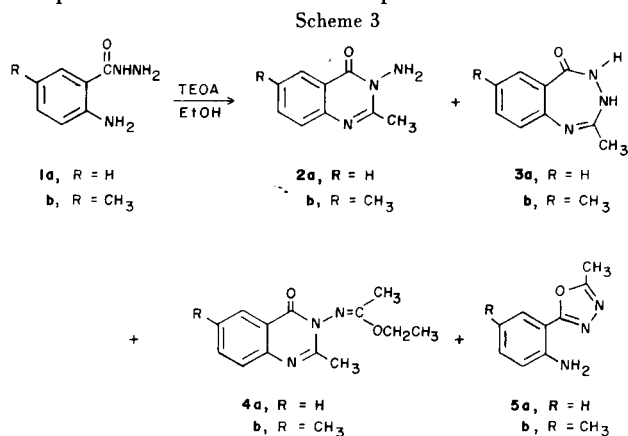
Table 1
4-(1,3,4-Oxadiazol-2-yl)-*N,N*-dialkylbenzenesulfonamides



II	R	R'	R ₂ N ₂ OS-orient.	Mp (°C)	Yield %	Analysis %					
						Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
a	Me	H	<i>meta</i>	129-130	89	47.42	4.38	16.59	47.30	4.39	16.66
b	Me	Me	<i>meta</i>	114-115	90	49.42	4.90	15.72	49.39	5.02	15.51
c	Me	Et	<i>meta</i>	87-89	100	51.23	5.37	14.94	51.20	5.33	14.83
d	Me	Ph	<i>meta</i>	168-169	96	58.34	4.59	12.76	58.37	4.76	13.02
e	Me	H	<i>para</i>	171.5-172.5	96	47.42	4.38	16.59	47.45	4.44	16.37
f	Me	Me	<i>para</i>	188-189	87	49.42	4.90	15.72	49.43	5.00	15.68
g	Me	Et	<i>para</i>	144-144.5	83	51.23	5.37	14.94	51.19	5.14	14.78
h	Me	Ph	<i>para</i>	201-203	99	58.34	4.59	12.76	58.30	4.66	12.65
i	Et	H	<i>meta</i>	124-125.5	81	51.23	5.37	14.94	51.10	5.50	14.74
j	Et	Me	<i>meta</i>	81.5-83	100	52.86	5.80	14.23	52.74	5.82	14.22
k	Et	Et	<i>meta</i>	76-78	93	54.35	6.19	13.58	54.37	6.23	13.54
l	Et	Ph	<i>meta</i>	110-112	80	60.48	5.36	11.76	60.40	5.39	11.78
m	Et	H	<i>para</i>	147.5-149	79	51.23	5.37	14.94	51.37	5.40	14.93
n	Et	Me	<i>para</i>	150-153.5	74	52.86	5.80	14.23	52.94	5.75	14.02
o	Et	Et	<i>para</i>	114-115	82	54.35	6.19	13.58	54.56	6.10	13.36
p	Et	Ph	<i>para</i>	147.5-150	96	60.48	5.36	11.76	60.57	5.46	11.78

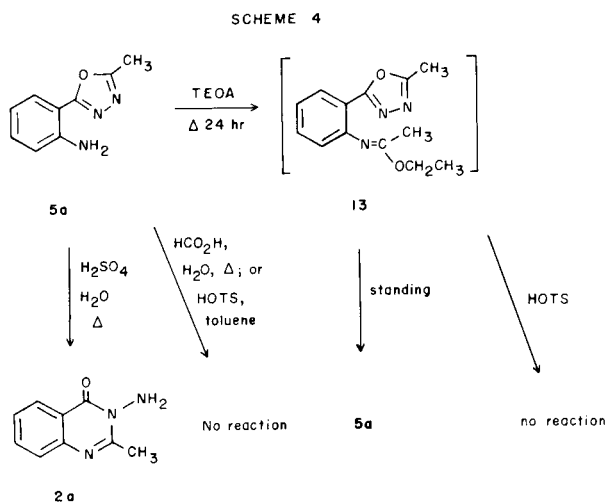


results with four equivalents of TEOA were obtained for comparison with the work of Merour [1], while the result with one equivalent of TEOA, which are markedly different, were gathered to gain a better understanding of the reaction. In most cases, chromatography was employed for separation and isolation of the products.



Results of Present Study

Compound	Yield (%)		Mp (°C)
	1 eq TEOA	4 eq TEOA	
2a	63	5	147-148
2b	61	—	170-171
3a	—	11	200-202
3b	6	8	250-252
4a	—	70	70-80
4b	—	55	128-129
5a	12	—	149-150
5b	20	—	182-184



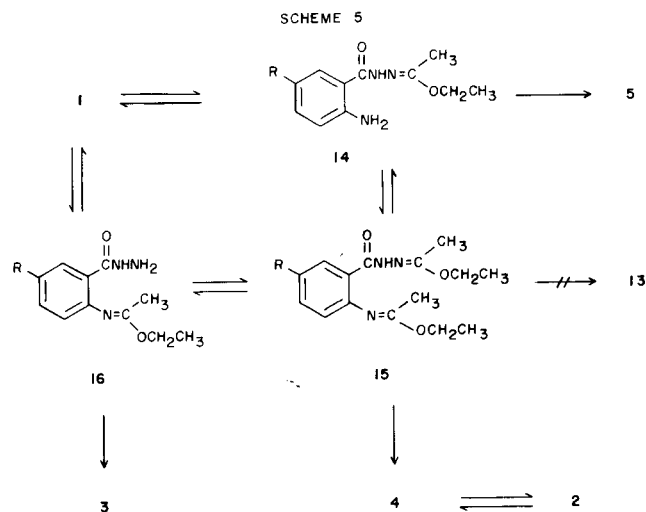
We obtained the same two products as did Merour [1] from the reaction of **1a** with four equivalents TEOA, namely, quinazolinone **2a** and benzotriazepinone **3a**. Benzotriazepinone **3b** was obtained from **1b** and TEOA under these same conditions, but the corresponding quinazolinone **2b** was not isolated. Physical constants were in agreement with the exception of compound **3b**, for which we found a melting point of 250-252°, compared to Merour's [1] melting point of 200°. However, the major products of these reactions, which we isolated in yields of 70% and 55%, respectively, were the respective imino ethers **4a** and **4b**. These products were not mentioned or isolated by Merour [1], possibly because they were very soluble in organic solvents and therefore not easily isolable by trituration or fractional recrystallization, and/or because they hydrolyzed or partially hydrolyzed to **2a** and **2b** during manipulation.

When **1a** was treated with only one equivalent of TEOA, quinazolinone **2a** was the major product (63%) and **4a** was absent. Benzotriazepinone **3a** was not isolated from this reaction, but 2-(5-methyl-1,3,4-oxadiazol-2-yl)benzenamine (**5a**) was obtained in 12% yield. Likewise, the 4-methyl analog of **5a** (**5b**) was obtained in 20% yield from the reaction of **1b** with one equivalent of TEOA, in addition to the major product, quinazolinone **2b** (61%), and benzotriazepinone **3b** (6%).

The results of Scheme 3 are intriguing, in that oxadiazole formation occurred with one equivalent of TEOA, but was suppressed with excess TEOA. We first thought that oxadiazole formation was occurring with excess TEOA and that the oxadiazole was then rearranging to another product (or other products) of the reaction. However, when we treated oxadiazole **5a** with excess TEOA for 24 hours (Scheme 4), no rearrangement occurred, and we isolated only the imino ether **13**. Imino ether **13** was characterized by spectral analysis, and was different from the isomeric imino ether **4a**. On storage, **13** reverted to **5a**. Although

2-(1,3,4-oxadiazol-2-yl)benzenamine has been rearranged [11] to 3-amino-4(3*H*)-quinazolinone with aqueous formic acid, oxadiazole **5a** was stable under these conditions. However, **5a** did rearrange to **2a** (64%) upon heating with aqueous sulfuric acid.

Since oxadiazole **5a** did not rearrange with excess TEOA and since we did not detect any of imino ether **13** in the product mixture from **1a** and four equivalents of TEOA, we felt there was another explanation for its absence in the reaction of **1a** with four equivalents of TEOA. In Scheme 5 we depict equilibria which could result from hydrazide **1** in the medium of ethanol and TEOA. The proportions of the various species which result should be dependent on the amount of TEOA, and we feel that the difference in stoichiometry (and not differences in thermodynamic stabilities of the products) explains the product distribution variance seen in Scheme 3. Imino ethers **4a** and **b** are produced in the reaction with four equivalents of TEOA, but not in the reaction with one equivalent. Perhaps oxadiazole formation requires a high concentration of intermediate **14**, which could result initially in the one-equivalent reaction, but may never be attained in the four-equivalent reaction.

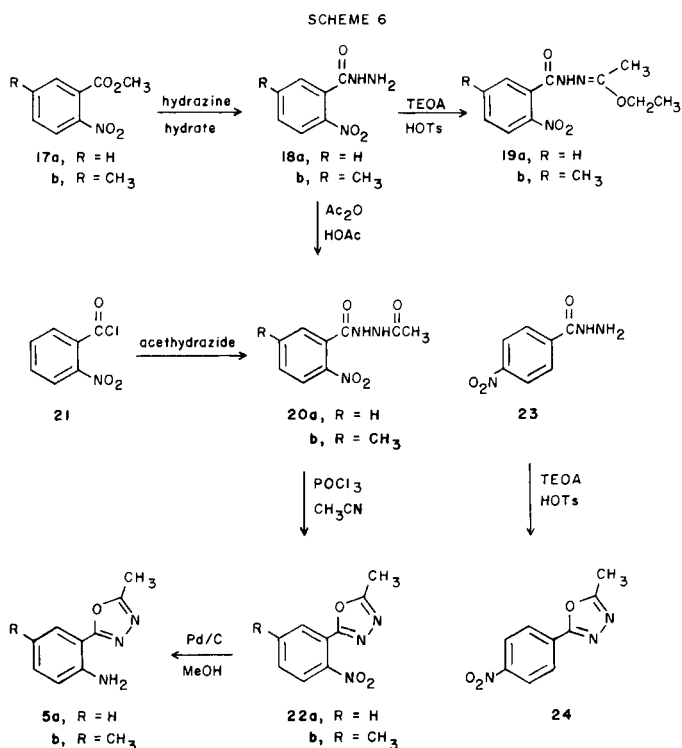


The structures of the reaction products of **1a** with TEOA (Scheme 3) were securely established. Aminoquinazolinone **2a** is well-known in the literature, and the reported physical constants were in agreement with those recorded for our sample. Reported syntheses for **2a** include (i) the treatment of 2-methyl-4(*H*)-1,3-benzoxazin-4-one with hydrazine [12]; (ii) heating methyl 2-(acetylamino)benzoate with hydrazine hydrochloride, phosphorous pentoxide and *N,N*-dimethylcyclohexylamine [13]; (iii) treating *o*-amino-benzoylhydrazine with ethyl acetoacetate [14]; (iv) fusion of 2-(acetylamino)benzoic acid with hydrazine [15]; and (v) successive treatment of methyl anthranilate with acetic anhydride and hydrazine hydrate [16].

The structures of benzotriazepinones **3a** and **b** were verified by their non-identity with the only other possible isomeric reaction products (*i.e.*, quinazolinones **1a** and **b** and oxadiazoles **5a** and **b**, respectively), the two dissimilar NH signals in the nmr spectra, and rearrangement studies (*vide infra*). Also, benzotriazepinones **3a** and **b** were characteristically high-melting, bright yellow compounds.

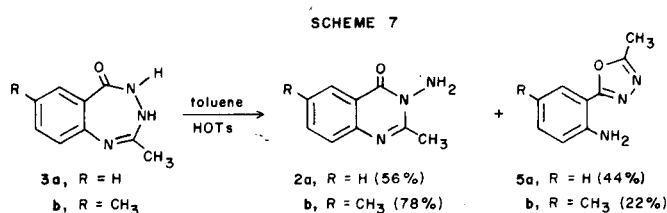
The structure of imino ether **4a** was verified by an alternate synthesis. Treatment of **2a** with excess, neat TEOA gave **4a**.

The structures of oxadiazoles **5a** and **b** were also established by alternate syntheses, as shown in Scheme 6. Since 2-nitrobenzoylhydrazines **18a** and **b** (which were prepared from methyl 2-nitrobenzoates **17a** and **b**, respectively) afforded only the respective imino ethers **19a** and **b** on treatment with TEOA and *p*-toluenesulfonic acid (HOTs) [17], we acylated hydrazide **18b** with acetic anhydride. The resulting diacylhydrazine **20b** was then cyclized, with phosphorous oxychloride in acetonitrile, to afford 2-methyl-5-(5-methyl-2-nitrophenyl)-1,3,4-oxadiazole (**22b**). Oxadiazole **22a** was prepared in similar fashion from diacylhydrazine **20a**, which was prepared directly from 2-nitrobenzoyl chloride (**21**) and acethydrazide. The nitrophenyloxadiazoles **22a** and **b** were cleanly reduced by catalytic hydrogenation to aminophenyloxadiazoles **5a** and **b**, respectively, which were identical in all respects with the products produced from **1a** and **1b**, respectively, and one equivalent of TEOA.



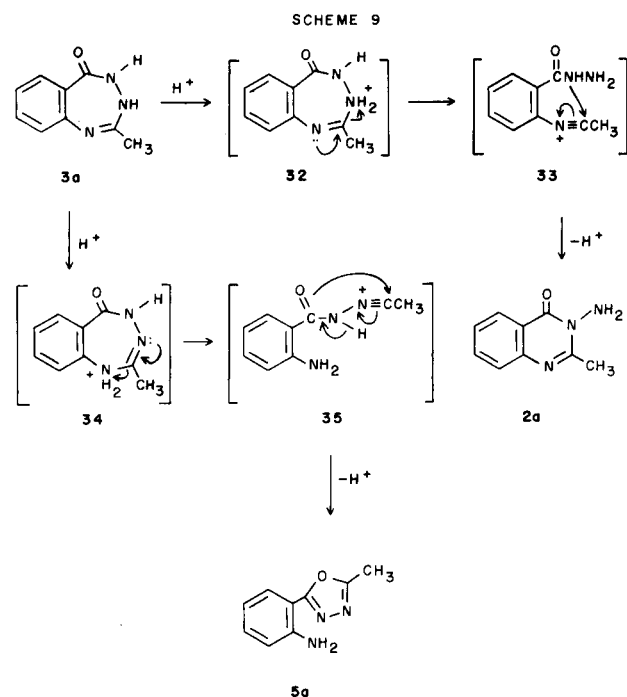
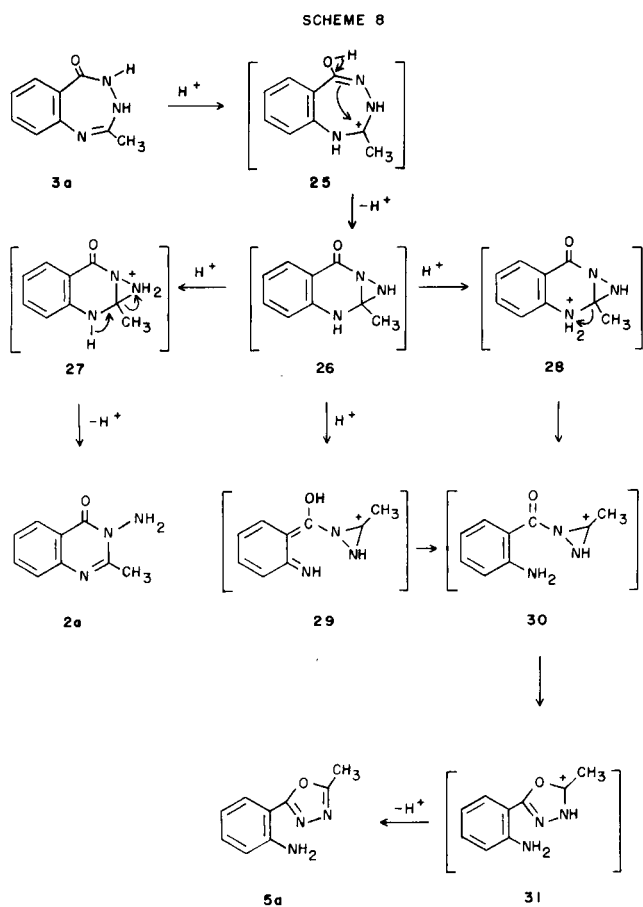
The failure of imino ethers **19a** and **b** to cyclize to oxadiazoles **22a** and **b**, respectively, under the reaction conditions in which they are formed, is an interesting result. When we treated 4-nitrobenzoylhydrazine (**23**) with TEOA and *p*-toluenesulfonic acid, oxadiazole **24** was cleanly produced (90% yield). Thus, steric factors and not electronic factors must be responsible for the lack of oxadiazole formation from **19a** and **b** [18]. The conversion of the electron-deficient arylhydrazine **23** to oxadiazole **24** fits well with the results of Table 1, wherein all of the arylhydrazines are similarly electron-deficient.

We have recently reported base-induced ring-contraction reactions of benzotriazepinediones [20]. Leiby and Heindel [21] have studied the base-induced rearrangements of 3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones [22, 23] and the related 3,4-dihydro systems [24]. All of these rearrangements produce 4(3*H*)-quinazolinones. In examining the behavior of benzotriazepinone **3a** with *p*-toluenesulfonic acid (HOTs) in toluene (Scheme 7), we found that a very clean and quantitative rearrangement took place, to give aminoquinazolinone **2a** (56%) and oxadiazole **5a** (44%). The identity of the two compounds in the mixture was determined by comparing the nmr (deuteriochloroform) spectrum of the mixture with those of the pure products, and percentages were determined from integrals. Since we did show that oxadiazole **5a** would rearrange to aminoquinazolinone **2a** with aqueous sulfuric acid, we felt it necessary to show that **5a** was stable to the rearrangement conditions. Indeed, when **5a** was exposed to the same conditions employed for the rearrangement it was recovered unchanged (Scheme 4).



One possible mechanism for this intriguing rearrangement of **3a** is depicted in Scheme 8. Protonated **3a** (ion **25**) could rearrange as shown to produce the pivotal and key diaziridine intermediate **26**. Protonation of the most basic diaziridine nitrogen atom would give ion **27**, which could undergo a 1,2-elimination sequence to give aminoquinazolinone **2a**. Alternatively, intermediate **26** could protonate at the arylamino site to give ion **28**, which could fragment as shown to give ion **30** (which could also be accessed through ion **29**). Ring-expansion of **30** to the protonated oxadiazole **31** would then lead to **5a**, after deprotonation.

Another potential mechanism for the rearrangement of **3a** is shown in Scheme 9, wherein rupture of the triazepinone ring (rather than ring contraction) is postulated, to produce nitrilium ions. Protonation of **3a** at the 3-position

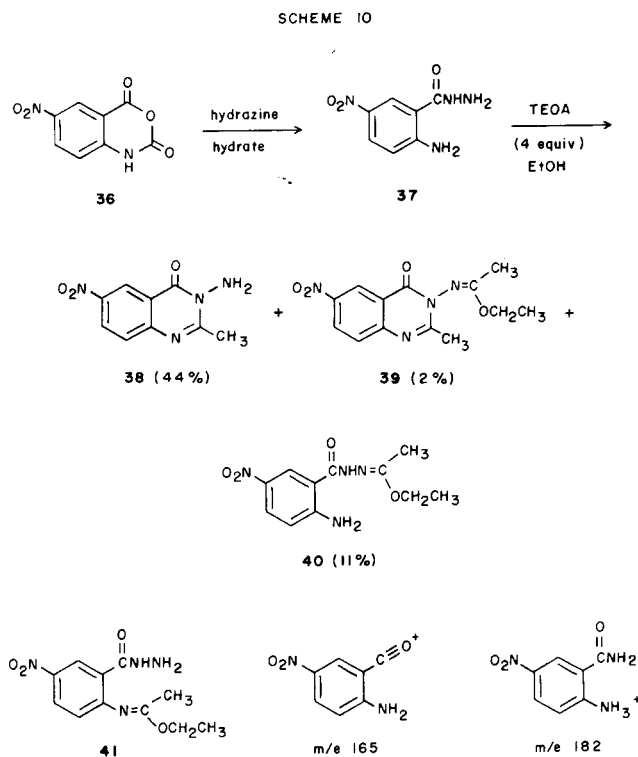


would produce ion **32**, which, upon scission of the 2,3-bond would generate nitrilium ion **33**. Recyclization of **33**, initiated by attack of the acyl-bearing nitrogen of the hydrazide on the nitrilium ion, would lead to aminoquinazolinone **2a**. In addition, protonation of **3a** at the 1-position (to give ion **34**) would lead to nitrilium ion **35**, after scission of the 1,2-bond. Cyclization of **35** with deprotonation, initiated by attack of the carbonyl oxygen on the nitrilium ion, would produce oxadiazole **5a**. This cyclization is a 5-*endo*-trigonal process, which is a favored mode of cyclization with respect to the Baldwin Rules for Ring Closure [25].

In addition to the obvious differences in the key intermediates of Schemes 8 and 9, there are inherently different electronic characteristics which they possess. Factors which would enhance the stability of ion **28** (Scheme 8), which is the protonated key intermediate **26**, should lead to a greater relative amount of oxadiazole **5a**. However, these same factors should also lead to a stabilization of nitrilium ion **33** (Scheme 9), which should produce a greater relative amount of aminoquinazolinone **2a**. The 7-methyl group in benzotriazepinone **3b** is positioned to stabilize both ions **28** and **33**. Since the rearrangement of **3b** produces a significantly *greater* amount of aminoquinazolin-

one (78%) and, conversely, a significantly *lesser* amount of oxadiazole (22%) than does **3a** (Scheme 7), we feel that the mechanism shown in Scheme 9 is the operative mechanism.

We did examine the reaction of one additional *o*-amino-benzoylhydrazide with TEOA. Treatment of 5-nitroisatoic anhydride (**36**) with hydrazine hydrate gave 2-amino-5-



nitrobenzoylhydrazine (**37**), which we treated with four equivalents of TEOA. We isolated three products from this reaction, as shown in Scheme 10. The major product, 3-amino-2-methyl-6-nitro-4(3*H*)-quinazolinone (**38**), was isolated in 44% yield. Also produced was a small amount of the corresponding imino ether **39** (2%). An 11% yield of a second imino ether was isolated, of empirical formula $C_{11}H_{14}N_4O_4$, to which we assigned structure **40**. The other possible structure which would fit this empirical formula is imino ether **41**, which we ruled out on the basis of mass spectral analysis. Fragments in the electron impact mass spectrum at m/e 165 and m/e 182 were consistent with structure **40** and not with structure **41**.

The lack of benzotriazepinone formation from hydrazide **37** and four equivalents of TEOA is reasonable in the context of the equilibria shown in Scheme 5. Formation of bisimino ether **15** ($R = NO_2$), which leads to quinazolinone **2** ($R = NO_2$, **38**), proceeds through imino ether **14** ($R = NO_2$, **40**), which is an observed product, rather than **16** ($R = NO_2$), which would lead to the absent benzotriazepinone. The nitro group electronically retards the rate of reaction of the anilino amino group with TEOA with respect to that of the hydrazide amino group, to effect this pathway differential. Thus, the observed products would be preferentially formed. Alternatively, the nitrobenzotriazepinone **3** ($R = NO_2$) may be formed to a minor extent, but in a reversible sense; the nitro group would enhance the electrophilicity of the 2-position, making the 2,1-bond susceptible to ethanol addition, which would lead back to **16** ($R = NO_2$).

In summary, our investigation of the reactions of *o*-aminobenzoyl hydrazines **1a** and **b** with four equivalents of TEOA was consistent with the recent report of Merour [1], in that aminoquinazolinones **2a** and **b** and benzotriazepinones **3a** and **b**, respectively, were produced. However, the major products which we isolated, the respective imino ethers **4a** and **b**, were not mentioned by Merour [1]. Oxadiazoles **5a** and **b**, respectively, were produced (only) when **1b** and **b** were treated with one equivalent of TEOA. Benzotriazepines **3a** and **b** rearranged, under conditions of acid-catalysis, to mixtures of aminoquinazolinones **2a**

and **b** and oxadiazoles **5a** and **b**, respectively. In the preparation of authentic samples of oxadiazoles **5a** and **b**, we found that *o*-nitrobenzoylhydrazines **18a** and **b** furnished imino ethers **19a** and **b**, respectively, rather than oxadiazoles when treated with TEOA. In contrast, *p*-nitrobenzoylhydrazine (**23**) gave oxadiazole **24** when treated with TEOA.

Thus, we can draw certain conclusions regarding the factors which influence oxadiazole formation in the systems we have studied. When anthranilhydrazides are treated with TEOA, oxadiazoles result if one equivalent of TEOA is used but not if excess (4 equivalents) is used. The

amount of TEOA presumably affects the proportions of various species present in a complex set of equilibria. *o*-Nitrobenzoylhydrazine will not undergo oxadiazole formation with TEOA, but *p*-nitrobenzoylhydrazine will. Steric effects and not electronic effects are, therefore, preventing the ortho isomer from cyclizing with TEOA. And finally, the latter point is embellished by the results shown in Table 1, where the benzoylhydrazines bearing strongly electron-withdrawing groups in the *meta* and *para* positions undergo efficient cyclization reactions with ortho esters to yield oxadiazoles.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with Perkin-Elmer Model 727B and Beckman Model 4240 spectrophotometers, nmr spectra with Varian EM-360A and Perkin-Elmer R-32 (90 MHz) spectrometers, and mass spectra with a Finnigan gc/ms Model 4023 (electron impact and chemical ionization) mass spectrometer. Combustion analyses for C, H and N were performed by Merrell Dow Analytical Laboratories, Cincinnati, OH.

Preparation of the 4-(1,3,4-Oxadiazol-2-yl)-*N,N*-dialkylbenzenesulfonamides (II) of Table 1, Exemplified by the Preparation of II.

A. 4-[(Dimethylamino)sulfonyl]benzoic Acid.

To an ice cold solution of 150 ml of 40% aqueous dimethylamine (Aldrich) was added, portionwise, 75.0 g (0.340 mole) of *p*-carboxybenzenesulfonyl chloride (Eastman). The addition was exothermic. After solution had occurred, the clear solution was diluted with an equal volume of water and acidified with concentrated hydrochloric acid. The resulting white precipitate was collected, air-dried and oven-dried to yield 77.2 g (99%) of 4-[(dimethylamino)sulfonyl]benzoic acid, mp 227-228° (lit [26] mp 255-256°); ir (Nujol): 3300-2300 (OH), 1690 (C=O) cm^{-1} nmr (deuteriochloroform and dimethylsulfoxide- d_6): δ 8.33 (d, $J = 9$ Hz, 2H, aromatic), 7.94 (d, $J = 9$ Hz, 2H, aromatic), 2.77 (s, 6H, NMe_2).

B. 4-[(Dimethylamino)sulfonyl]benzoic Acid Ethyl Ester.

A slurry of 69.0 g (0.301 mole) of 4-[(dimethylamino)sulfonyl]benzoic acid in 500 ml of ethanol was saturated with hydrogen chloride gas and heated at reflux for 15 hours. The solution was cooled and refrigerated and the resulting white needles were collected and air-dried to yield 56.2 g (72%) of 4-[(dimethylamino)sulfonyl]benzoic acid ethyl ester, mp 100-101°; ir (Nujol): 1715 (C=O) cm^{-1} ; nmr (deuteriochloroform): δ 8.34 (d, $J = 8$ Hz, 2H, aromatic), 7.97 (d, $J = 8$ Hz, 2H, aromatic), 4.50 (q, $J = 7.2$ Hz, 2H, CH_2), 2.83 (s, 6H, NMe_2), 1.45 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3).

Anal. Calcd. for $C_{11}H_{15}NO_4S$: C, 51.34; H, 5.88; N, 5.44. Found: C, 51.07; H, 5.91; N, 5.71.

C. 4-[(Dimethylamino)sulfonyl]benzoic Acid Hydrazide (I, $R = CH_3$).

A mixture of 44.4 g (0.173 mole) of 4-[(dimethylamino)sulfonyl]benzoic acid ethyl ester and 230 ml of hydrazine hydrate was heated until solution resulted. The solution was cooled, diluted with 250 ml of water and the resulting white, crystalline solid was collected and air-dried to yield 40.4 g (96%) of I ($R = CH_3$), mp 204-206°; ir (Nujol): 3370 and 3275 (NH), 1665 (C=O) cm^{-1} ; nmr (deuteriochloroform and dimethylsulfoxide- d_6): δ 9.9 (very broad s, 1H, NH, deuterium oxide-exchangeable), 8.20 (d, $J = 8.5$ Hz, 2H, aromatic), 7.87 (d, $J = 8.5$ Hz, 2H, aromatic), 4.5 (very broad s, 2H, NH_2 , deuterium oxide-exchangeable), 2.70 (s, 6H, NMe_2).

Anal. Calcd. for $C_9H_{13}N_3O_3S$: C, 44.43; H, 5.38; N, 17.27. Found: C, 44.51; H, 5.18; N, 17.32.

D. 4-(1,3,4-Oxadiazol-2-yl)-*N,N*-dimethylbenzenesulfonamide (III).

A solution of 7.30 g (30.0 mmoles) of I ($R = CH_3$) and 25 ml of triethyl orthoacetate in 50 ml of ethanol was heated at reflux. Progress of the re-

action was monitored by tlc. After 4 days, the reaction was ca. 50% complete, and a solid was present. After 8 days, the mixture was cooled and the solid was collected and air-dried to give 7.01 g (87%) if III, mp 188-189° (ethanol); ir (Nujol): 1340, 1155, 950, 760 cm^{-1} ; nmr (dimethylsulfoxide- d_6): δ 8.25 (d, $J = 8.5$ Hz, 2H, aromatic), 7.95 (d, $J = 8.5$ Hz, 2H, aromatic), 2.69 (s, 6H, NMe_2), 2.63 (s, 3H, ArCH_3).

Anal. Calcd. for $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_3\text{S}$: C, 49.42; H, 4.90; N, 15.72. Found: C, 49.43; H, 5.00; N, 15.68.

Treatment of 2-Aminobenzoic Acid Hydrazide (**1a**) with One Equivalent of Triethyl Orthoacetate.

A solution of 1.51 g (0.100 mole) of **1a** [27] and 1.62 g (0.100 mole) of triethyl orthoacetate in 50 ml of ethanol was heated at reflux for 16 hours. The volume was reduced to half, and the crystals which formed were collected, washed with chloroform and dried to give 0.830 g of 3-amino-2-methyl-4(3*H*)-quinazolinone (**2a**), mp (ethanol) 147-148° (lit [15] mp 148-149°); ir (Nujol): 3320 and 3220 (NH), 1670 (C=O), 1610 (C=N) cm^{-1} ; nmr (deuteriochloroform): δ 8.24-8.00 (m, 1H, H at 5-position), 7.70-7.20 (m, 3H, remaining aromatic), 4.87 (s, 2H, NH_2), 2.68 (s, 3H, CH_3); ms: (70 eV, electron impact) m/e 175 (molecular ion).

Anal. Calcd. for $\text{C}_9\text{H}_9\text{N}_3\text{O}$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.60; H, 5.02; N, 24.35.

The filtrate from above was concentrated and the residue was triturated with ether. The resulting solid (0.430 g, after collection and drying) was applied in a small volume of chloroform to a 150-g column of Silica Gel 60 (70-230 mesh, EM Reagents) which had been slurry-packed with chloroform. After elution of a 1-liter forerun, 18 100-ml fractions were collected. Fractions 3-6 were combined and concentrated to leave a 0.210 g (12%) of 2-(5-methyl-1,3,4-oxadiazol-2-yl)benzenamine (**5a**), mp 149-150° (ethanol); ir (Nujol): 3480-3150 (NH), 1630, 1600 cm^{-1} ; nmr (deuteriochloroform): δ 7.75-7.52 (m, 1H, H at 3-position), 7.37-7.03 (m, 1H, H at 5-position), 6.83-6.47 (m, 2H, protons at 4- and 6-positions), 5.77 (broad s, 2H, NH_2), 2.57 (s, 3H, CH_3); ms: (70 eV, electron impact) m/e 175 (molecular ion).

Anal. Calcd. for $\text{C}_9\text{H}_9\text{N}_3\text{O}$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.46; H, 5.16; N, 24.00.

Fractions 9-15 were combined and concentrated to leave 0.270 g of additional **2a**, mp 146.5-147.5° (ethanol). Total yield of **2a** was 1.19 g (63%).

Treatment of 2-Aminobenzoic Acid Hydrazide (**1a**) with Four Equivalents of Triethyl Orthoacetate.

A solution of 1.51 g (10.0 mmoles) of **1a** [27] and 6.49 g (40.0 mmoles) of triethyl orthoacetate in 50 ml of ethanol was heated at reflux for 16 hours. Solution was concentrated to leave 3.77 g of material which was applied, in a minimum volume of chloroform, to a 150-g column of Silica Gel 60 (EM Reagents, 70-230 mesh). The column was eluted with 500 ml of chloroform, followed by seven 500-ml volumes of chloroform containing methanol in amounts increasing incrementally between 1% and 2%. After elution of 1500 ml of forerun, 25 100-ml fractions were collected. Fractions 2-6 were combined and concentrated to leave 1.72 g (70%) of *N*-(2-methyl-4-oxo-3(4*H*)-quinazolinyl)ethanimidic acid (**4a**), which crystallized on standing to a white, waxy solid, mp 70-80°; ir (Nujol): 1675 (C=O), 1605 (C=N) cm^{-1} ; nmr (deuteriochloroform): δ 8.33-8.10 (m, 1H, H at 5-position), 7.77-7.23 (m, 3H, remaining aromatic), 4.40 (q, $J = 7$ Hz, 2H, CH_2), 2.48 (s, 3H, CH_3), 1.88 (s, 3H, CH_3), 1.40 (t, $J = 7$ Hz, CH_2CH_3); ms: (70 eV, chemical ionization, methane) 246 ($\text{M}^+ + 1$), 274 ($\text{M}^+ + 29$), 286 ($\text{M}^+ + 41$).

Anal. Calcd. for $\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.46; H, 6.28; N, 16.85.

An authentic sample of **4a** was prepared as follows. An 810-mg (4.62 mmoles) quantity of **2a** was mixed with 20 ml of triethyl orthoacetate and the mixture was heated at reflux for 2.5 hours. The tlc of the solution showed the absence of **2a**. The solution was thoroughly concentrated and the residue was oven-dried to give 1.02 g (90%) of **4a**. The infrared (Nujol) and nmr (deuteriochloroform) spectra of this sample of **4a** were identical to those of **4a** isolated from the column.

Fraction 8 was concentrated, the residue was triturated with ether and

the white needles were collected to give 90 mg (5%) of **2a**, mp 146-147°.

Fractions 17-23 were combined and concentrated to leave 0.190 g (11%) of 3,4-dihydro-2-methyl-5*H*-1,3,4-benzotriazepin-5-one (**3a**), mp 200-202° (ethanol); ir (Nujol): 3300 (NH), 1690 (sh), 1620, 1605 (sh) cm^{-1} ; nmr (deuteriochloroform): δ 8.50 (broad s, 1H, NH), 7.87-7.50 (m, 2H, NH and H at 6-position), 7.36-7.04 (m, 1H, H at 8-position), 6.97-6.60 (m, 2H, protons at 7- and 9-positions), 1.97 (s, 3H, CH_3); ms: (70 eV, chemical ionization, methane) 176 ($\text{M}^+ + 1$), 204 ($\text{M}^+ + 29$), 216 ($\text{M}^+ + 41$).

Anal. Calcd. for $\text{C}_9\text{H}_9\text{N}_3\text{O}$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.62; H, 5.10; N, 24.10.

Treatment of 2-Amino-5-methylbenzoic Acid Hydrazide (**1b**) with One Equivalent of Triethyl Orthoacetate.

A solution of 1.65 g (10.0 mmoles) of **1b** [28] and 1.62 g (10.0 mmoles) of triethyl orthoacetate in 50 ml of ethanol was heated at reflux for 16 hours. The solution was concentrated to dryness, and the resulting 2.00 g of material was dissolved in ethanol (25 ml) and allowed to cool. The yellow solid was collected to give ca. 500 mg of 3,4-dihydro-2,7-dimethyl-5*H*-1,3,4-benzotriazepin-5-one (**3b**), mp 250-252° (after another recrystallization from ethanol); ir (Nujol): 3290 (NH), 1690, 1630, 1605 cm^{-1} ; nmr (dimethylsulfoxide- d_6): δ 9.27 (s, 1H, NH), 7.97 (s, 1H, NH), 7.55-7.45 (m, 1H, H at 6-position), 7.16-6.95 (m, 1H, H at 8-position), 6.70 (d, $J = 8$ Hz, 1H, H at 9-position), 2.15 (s, 3H, CH_3), 1.88 (s, 3H, CH_3); ms: (70 eV, chemical ionization, methane) 190 ($\text{M}^+ + 1$), 218 ($\text{M}^+ + 29$), 230 ($\text{M}^+ + 41$).

Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.26; H, 5.80; N, 22.51.

Another 2.00 g of material was generated as above and applied, as a chloroform-ethanol solution, to a 150-g column of Silica Gel 60 (EM Reagents, 70-230 mesh) which had been slurry-packed with chloroform. Elution was accomplished with one liter of chloroform followed by seven 500-ml volumes of chloroform containing methanol, incrementally increasing from 1% to 2%. After collecting a forerun of 2300 ml, 22 100-ml fractions were collected. Fraction 1 was collected and concentrated to leave 20.0 mg of 4-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)benzenamine (**5b**), mp 178-182°; mp 182-184° (ethanol); ir (Nujol): 3430, 3315 and 3210 (NH_2), 1630, 1590 cm^{-1} ; nmr (deuteriochloroform): δ 7.44 (d, $J = 2$ Hz, 1H, H at 3-position), 7.02 (d of d, $J_{5,3} = 2$ Hz, $J_{5,6} = 8$ Hz, 1H, H at 5-position), 6.62 (d, $J = 8$ Hz, 1H, H at 6-position), 5.60 (broad signal, 2H, NH_2 , deuterium oxide-exchangeable); ms: (70 eV, electron impact) m/e 189 (molecular ion).

Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.49; H, 5.90; N, 22.34.

Fractions 6 and 7 were combined and concentrated to leave 0.230 g of 2,6-dimethyl-4(3*H*)-quinazolinone (**2b**), mp 170-171° (ethanol); ir (Nujol): 3290, 3240 and 3200 (NH_2), 1670 (C=O), 1630, 1605 cm^{-1} ; nmr (deuteriochloroform): δ 8.00-7.84 (m, 1H, H at 5-position), 7.53-7.40 (m, 2H, protons at 7- and 8-positions), 4.86 (s, 2H, NH_2), 2.65 (s, 3H, CH_3), 2.43 (s, 3H, CH_3); ms: (70 eV, electron impact) m/e 189 (molecular ion).

Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.19; H, 5.79; N, 22.41.

Fractions 2-5 were combined and concentrated to leave 1.29 g of a 28:72 mixture of **5b:2b**, as determined from nmr integrals. Thus, the total yield of **5b** from the column was 0.380 g (20%), and the total yield of **2b** was 1.16 g (61%).

Fractions 15-22 were combined and concentrated to leave 0.120 g (6%) of **3b**, whose infrared and mass spectra were identical to those of **3b** isolated by fractional recrystallization.

Treatment of 2-Amino-5-methylbenzoic Acid Hydrazide (**1b**) with Four Equivalents of Triethyl Orthoacetate.

A solution of 1.65 g (10.0 mmoles) of **1b** [28] and 6.49 g (40.0 mmoles) of triethyl orthoacetate in 50 ml of ethanol was heated at reflux for 16 hours. The solution was concentrated to dryness and the residue was treated with a small volume of ethanol to yield a mixture of white and yellow crystals. This mixture was treated with chloroform to dissolve the white crystals and the yellow crystals were collected to give 0.160 g (8%)

of **3b**, mp 238-240°; the infrared, nmr and mass spectra for this sample of **3b** were identical to those of **3b** isolated from the reaction with one equivalent of triethyl orthoacetate.

Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.07; H, 5.76; N, 21.94.

The filtrate from above was evaporated to dryness and the residue was recrystallized from ethanol to give 1.42 g (55%) of *N*-2,6-dimethyl-4-oxo-3(4*H*)-quinazoliny]ethanimidic acid ethyl ester (**4b**) as a white, crystalline solid, mp 128-129°; ir (Nujol): 1675 (C=O), 1615 (sh), 1695 cm^{-1} ; nmr (dimethylsulfoxide- d_6): δ 7.95-7.80 (m, 1H, H at 5-position), 7.65-7.37 (m, 2H, protons at 7- and 8-positions), 4.36 (q, $J = 7$ Hz, 2, CH_2), 2.40 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 1.34 (t, $J = 7$ Hz, 3, OCH_2CH_3); ms: (70 eV, chemical ionization, methane) 260 ($M^+ + 1$), 288 ($M^+ + 29$), 300 ($M^+ + 41$).

Anal. Calcd. for $C_{14}H_{17}N_3O_2$: C, 64.84; H, 6.61; N, 16.21. Found: C, 64.83; H, 6.57; N, 16.39.

Treatment of 2-(5-Methyl-1,3,4-oxadiazol-2-yl)benzenamine (**5a**) with Various Reagents (Scheme 4).

A. With Triethyl Orthoacetate.

A solution of 500 mg (2.85 mmoles) of **5a** in 25 ml of triethyl orthoacetate was heated at reflux for 24 hours. The excess triethyl orthoacetate was removed by Kugelrohr distillation to leave a quantitative yield of *N*-[2-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]ethanimidic acid ethyl ester (**13**) as a viscous liquid; ir (neat): 1670 (C=N) cm^{-1} ; nmr (deuteriochloroform): δ 7.97-7.74 (m, 1H, H at 3-position), 7.53-7.00 (m, 2H, protons at 5- and 6-positions), 6.97-6.67 (m, 1H, H at 4-position), 4.23 (q, $J = 7$ Hz, 2H, CH_2), 2.53 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 1.33 (t, $J = 7$ Hz, 3H, CH_2CH_3); ms: (70 eV, electron impact) m/e 245 (molecular ion).

On standing, **13** converted to a white solid. Recrystallization (ether-hexane) afforded **5a**, mp 144-145°; ir (Nujol) of this sample was identical to that of the starting material.

Anal. Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.67; H, 5.31; N, 23.74.

B. With Formic Acid.

A mixture of 300 mg (1.71 mmoles) of **5a**, 5 ml of water and 10 drops of formic acid was placed in an oil bath at 155-160° for 10 minutes. The mixture was cooled, triturated with water and the solid was collected and air-dried to yield 0.260 g (87%) of recovered **5a**, as shown by infrared spectroscopy.

C. With *p*-Toluenesulfonic Acid.

A solution of 200 mg (1.14 mmoles) of **5a** in 25 ml of toluene containing a few mg of *p*-toluenesulfonic acid was heated at reflux for 90 minutes. The solution was concentrated and the residue was triturated with water. The solid was collected and air-dried to afford a quantitative recovery of **5a**, as shown by infrared spectroscopy.

D. With Sulfuric Acid.

A mixture of 0.250 g (1.43 mmoles) of **5a**, 10 ml of water and 10 drops of concentrated sulfuric acid was placed in an oil bath at 140° for 1 hour. The concentrated mixture was cooled, diluted with water and basified with aqueous sodium bicarbonate. The solid was collected, washed with water and air-dried to yield 0.160 g (64%) of **2a** (as shown by ir), mp 148-149° (ethanol-water).

Anal. Calcd. for $C_9H_9N_3O$: C, 61.73; H, 5.18; N, 23.99. Found: C, 61.49; H, 5.24; N, 23.85.

5-Methyl-2-nitrobenzoic Acid Methyl Ester (**17b**).

A solution of 102 g (0.563 mole) of 2-nitro-5-methylbenzoic acid (Chemical Procurement Laboratories) in 750 ml of methanol was treated with gaseous hydrogen chloride for 10 minutes. The warm solution was heated at reflux for 20 hours and concentrated to dryness to leave 109 g (99%) of **17b**, mp 77-79° (methanol) (lit [29] mp 78-79°); ir (Nujol): 1725 (C=O), 1550, 1315 and 850 (NO_2) cm^{-1} ; nmr (deuteriochloroform): δ 7.77 (d, $J =$

8 Hz, 1H, H at 3-position), 7.50-7.24 (m, 2H, protons at 4- and 6-positions), 3.87 (s, 3H, OCH_3), 2.45 (s, 3H, $ArCH_3$).

5-Methyl-2-nitrobenzoic Acid Hydrazide (**18b**).

A mixture of 77.6 g (0.398 mole) of **17b**, 100 ml of hydrazine hydrate and 50 ml of water was heated to reflux and the resulting solution was maintained at reflux for 20 hours. The coffee colored solution was diluted with 200 ml of water while still hot and the white, fluffy needles which resulted on cooling were collected and air-dried to yield 53.3 g (69%) of **18b**, mp 145-147°; ir (Nujol): 3300 (NH), 1630 (C=O), 1520, 1365 and 840 (NO_2) cm^{-1} ; nmr (deuteriochloroform and dimethylsulfoxide- d_6): δ 9.33 (broad s, 1H, NH), 7.93-7.70 (m, 1H, H at 3-position), 7.10-7.40 (m, 2H, protons at 4- and 6-positions), 4.03 (broad signal, 2H, NH_2), 2.40 (s, 3H, CH_3); ms (70 eV, electron impact) m/e 295 (molecular ion).

Anal. Calcd. for $C_9H_9N_3O_3$: C, 49.23; H, 4.65; N, 21.53. Found: C, 49.06; H, 4.63; N, 21.69.

N-[2-Nitrobenzoyl]amino]ethanimidic Acid Ethyl Ester (**19a**).

A mixture of 10.0 g (55.2 mmoles) of 2-nitrobenzoylhydrazine (**18a**) [6] and 50 ml of triethyl orthoacetate was heated at reflux for 1 hour. Solid was present in the mixture at all times [17]. The solid was collected, washed with ether and air-dried to give 13.2 g (95%) of **19a**, mp 153-154° (ethanol); ir (Nujol): 3290 (NH), 1630 (C=O), 1605 cm^{-1} ; nmr (dimethylsulfoxide- d_6): δ 8.15-7.40 (m, 4H, aromatic), 4.12 and 3.47 (quartets, $J = 7$ Hz, 2H, CH_2), 2.88 and 2.93 (singlets, 3H, $N=CCH_3$), 1.22 and 0.87 (triplets, $J = 7$ Hz, 3H, CH_2CH_3); ms: (70 eV, chemical ionization, methane) 252 ($M^+ + 1$), 280 ($M^+ + 29$), 292 ($M^+ + 41$).

Anal. Calcd. for $C_{11}H_{13}N_3O_4$: C, 52.58; H, 5.22; N, 16.73. Found: C, 52.46; H, 5.20; N, 16.70.

2-Amino-5-methylbenzoic Acid (1-Ethoxyethylidene)hydrazide (**19b**).

A mixture of 10.0 g (51.2 mmoles) of **18b**, 50 ml of triethyl orthoacetate and a few mg of *p*-toluenesulfonic acid was heated at reflux for 15 hours. The new mixture (clear supernatant plus lump of yellow solid) was cooled and more yellow solid precipitated. The crystalline solid was collected, washed with ethanol and oven-dried to yield 12.7 g (94%) of **19b**, mp 157-158°; ir (potassium bromide): 3290 and 3070 (NH), 1650 (broad C=O), 1525, 1360 and 855 (NO_2) cm^{-1} ; nmr (dimethylsulfoxide- d_6): δ 10.43 (s, 1H, NH), 7.95 (d, $J = 9$ Hz, 1H, H at 3-position), 7.55-7.25 (m, 2H, protons at 4- and 6-positions), 4.12 and 3.48 (quartets, $J = 7.5$ Hz, 2H, OCH_2), 2.40 (s, 3H, $ArCH_3$), 2.06, 1.95, 1.89 and 2.75 (singlets, 3H, $N=CCH_3$), 1.23 and 0.89 (triplets, $J = 7.5$ Hz, 3H, OCH_2CH_3); ms: (70 eV, chemical ionization, methane) 266 ($M^+ + 1$), 294 ($M^+ + 29$), 306 ($M^+ + 41$).

Anal. Calcd. for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.36; H, 5.70; N, 16.12.

2-Nitrobenzoic Acid 2-Acetylhydrazide (**20a**).

To an ice cold solution of 38.7 g (0.522 mole) of acetylhydrazide in 200 ml of methylene chloride was added a solution of 48.4 g (0.261 mole) of 2-nitrobenzoyl chloride (**21**) in 100 ml of methylene chloride, at a rate such that the temperature was kept below 20°. After 2 hours the mixture was treated with 200 ml of water and the solid was collected and oven-dried to give 33.5 g (57%) of **20a**, mp 200-201° (ethanol); ir (Nujol): 3200 (NH), 1600 (C=O) cm^{-1} ; nmr (dimethylsulfoxide- d_6): δ 10.42 (s, 1H, NH), 10.03 (s, 1H, NH), 8.17-7.59 (m, 2H, aromatic), 1.90 (s, 3H, CH_3).

Anal. Calcd. for $C_9H_9N_3O_4$: C, 48.43; H, 4.06; N, 18.93. Found: C, 48.23; H, 4.13; N, 19.13.

2-Nitro-5-methylbenzoic Acid 2-Acetylhydrazide (**20b**).

To a solution of 30.0 g (0.154 mole) of **18b** in 200 ml of acetic acid was added 20.4 g (0.200 mole) of acetic anhydride. The addition was exothermic and after a few minutes, a white, crystalline, voluminous solid appeared. The mixture was heated at reflux for one hour and the solution was diluted while hot with 400 ml of water and allowed to crystallize. The white needles were collected, washed with water and oven-dried to yield 27.7 g (76%) of **20b**, mp 221-222°; ir (potassium bromide): 3200 (NH), 1600, 1580, 1515 (NO_2), 1365 (NO_2), 855 (NO_2) cm^{-1} ; nmr (deuteriochloro-

form and dimethylsulfoxide- d_6): δ 10.23 (s, 1H, NH), 10.06 (s, 1H, NH), 7.87 (d, $J = 8$ Hz, 1H, H at 3-position), 7.47-7.13 (m, 2H, protons at 4- and 6-positions), 2.44 (s, 3H, CH_3 at 5-position), 2.00 (s, 3H, COCH_3); ms: (70 eV, chemical ionization, methane) 238 ($M^+ + 1$), 266 ($M^+ + 29$), 278 ($M^+ + 41$).

Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_4$: C, 50.63; H, 4.67; N, 17.72. Found: C, 50.27; H, 4.50; N, 18.08.

2-Methyl-5-(2-nitrophenyl)-1,3,4-oxadiazole (**22a**).

A mixture of 11.2 g (50.0 mmoles) of **20a**, 8.43 g (55.0 mmoles) of phosphorus oxychloride and 100 ml of acetonitrile was heated at reflux for 2.5 hours. Solid was always present in the reaction mixture. The mixture was concentrated and triturated with water. The solid was collected and air-dried to give 3.40 g (33%) of **22a**, mp 94-95° (water); ir (Nujol): 1535, 1360 and 840 (NO_2) cm^{-1} ; nmr (dimethylsulfoxide- d_6): δ 8.20-7.70 (m, 4H, aromatic), 2.51 (s, 3H, CH_3); ms: (70 eV, chemical ionization, methane) 206 ($M^+ + 1$), 234 ($M^+ + 29$), 246 ($M^+ + 41$).

Anal. Calcd. for $\text{C}_9\text{H}_7\text{N}_3\text{O}_3$: C, 52.68; H, 3.44; N, 20.48. Found: C, 52.28; H, 3.49; N, 20.45.

2-Methyl-5-(5-methyl-2-nitrophenyl)-1,3,4-oxadiazole (**22b**).

A mixture of 27.7 g (0.117 mole) of **20b**, 19.9 g (0.130 mole) of phosphorus oxychloride and 250 ml of acetonitrile was heated at reflux. After 30 minutes, solution resulted. After 2 hours at reflux, the solution was concentrated and the solid residue was treated with water. After the trituration was complete, the solid was collected and oven-dried to yield 22.4 g (87%) of crude **22b**. Recrystallization from ethanol gave a mixture of white and yellow crystals. Recrystallization from ethanol-water gave **22b** as white, fluffy needles, mp 99-101°; ir (potassium bromide): 1520, 1345 and 845 (NO_2) cm^{-1} ; nmr (deuteriochloroform): δ 7.90 (d, $J = 9$ Hz, 1H, H at 3-position), 7.70-7.30 (m, 2H, protons at 4- and 6-positions), 2.60 (s, 3H, CH_3), 2.50 (s, 3H, CH_3); ms: (70 eV, electron impact) m/e 219 (molecular ion). Another recrystallization for elemental analysis gave **22b** as white, fluffy needles, mp 101-102°.

Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_3$: C, 54.79; H, 4.14; N, 19.17. Found: C, 54.53; H, 4.06; N, 19.39.

2-(5-Methyl-1,3,4-oxadiazol-2-yl)benzenamine (**5a**) from **22a**.

A solution of 5.40 g (26.3 mmoles) of **22a** in 100 ml of methanol was treated with 100 mg of 5% Pd/C and hydrogenated in a Parr apparatus at ca. 50 psi until hydrogen uptake ceased. The catalyst was removed by filtration, the filtrate was concentrated to dryness and the residue was recrystallized from ethanol to give 3.30 g (71%) of **5a**, mp 148-149°; the infrared, nmr and mass spectra for this sample of **5a** were identical to those of **5a** isolated by chromatography from the reaction of **1a** with one equivalent of triethyl orthoacetate.

Anal. Calcd. for $\text{C}_9\text{H}_9\text{N}_3\text{O}$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.46; H, 5.16; N, 24.00.

4-Methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)benzenamine (**5b**) from **22b**.

A solution of 8.00 g (36.5 mmoles) of **22b** in 150 ml of methanol was treated with 500 mg of 10% Pd/C and hydrogenated in a Parr apparatus for one hour, at which time hydrogen uptake had ceased. The product was insoluble in the resulting mixture, so the catalyst and product were collected by filtration and the product was separated by successive extractions with hot ethanol. The combined filtrates were concentrated to leave 6.81 g (99%) of **22b** as a white solid, mp 182-184° (ethanol). The infrared spectrum for this sample of **5b** was identical to that of **5b** isolated by chromatography from the reaction of **1b** with one equivalent of triethyl orthoacetate.

4-Nitrobenzoic Acid Hydrazide (**23**).

To a solution of 39.0 g (0.200 mole) of ethyl *p*-nitrobenzoate in 150 ml of ethanol was added 11.0 g (0.220 mole) of hydrazine hydrate, and the resulting solution was heated at reflux for 15 hours. The solution was cooled and the resulting fine, yellow prisms were collected, washed with ethanol and air-dried to give 29.5 g (74%) of **23**, mp 213-214° (lit [30] mp

210°); nmr (dimethylsulfoxide- d_6): δ 10.10 (broad s, 1H, CONH), 8.43-7.90 (m, 4H, aromatic), 4.63 (broad s, 2H, NH_2); ms: (70 eV, electron impact) m/e 181 (molecular ion).

When excess hydrazine hydrate was employed with ethyl *p*-nitrobenzoate, reduction of the nitro group occurred in addition to hydrazine formation. Thus, a mixture of 46.0 g (0.236 mole) of ethyl *p*-nitrobenzoate, 100 ml of hydrazine hydrate and 50 ml of water was heated at reflux for 68 hours. The clear solution was diluted while hot with 100 ml of water, filtered and cooled. The clear rods which separated were collected and oven-dried to yield 21.6 g (61%) of 4-aminobenzoic acid hydrazide, mp 222-226° (lit [31] mp 220° dec); nmr (dimethylsulfoxide- d_6): δ 9.33 (s, 1H, CONH), 7.77-7.44 (m, 2H, protons at 3- and 5-positions), 6.73-6.40 (m, 2H, protons at 2- and 6-positions), 5.60 (s, 2H, NH_2), 4.30 (broad s, 2H, NH_2); ms: (70 eV, chemical ionization, methane) 152 ($M^+ + 1$), 180 ($M^+ + 29$), 192 ($M^+ + 41$).

2-Methyl-5-(4-nitrophenyl)-1,3,4-oxadiazole (**24**).

A mixture of 10.0 g (55.2 mmoles) of **23**, 50 ml of triethyl orthoacetate and a few mg of *p*-toluenesulfonic acid was heated at reflux for 15 hours. During the first few minutes the nature of the precipitate changed, becoming voluminous. At the end of the reflux period, the nature of the precipitate had again changed, to granular. The mixture was cooled and more crystals (yellow needles) separated. The solid was collected, washed with ethanol and oven-dried to give 10.2 g (90%) of **24**, mp 169-170° (methanol); nmr (deuteriochloroform): δ 8.39-8.04 (m, 4H, aromatic), 2.59 (s, 3H, CH_3); ms: (70 eV, electron impact) m/e 205 (molecular ion).

Anal. Calcd. for $\text{C}_9\text{H}_7\text{N}_3\text{O}_3$: C, 52.68; H, 3.44; N, 20.48. Found: C, 52.34; H, 3.46; N, 20.34.

Rearrangement of 3,4-Dihydro-2-methyl-5*H*-1,3,4-benzotriazepin-5-one (**3a**) with *p*-Toluenesulfonic Acid.

A solution of 500 mg (2.85 mmoles) of **3a** in 25 ml of toluene containing a few mg of *p*-toluenesulfonic acid was heated at reflux for 90 minutes. The solution was concentrated to leave 0.500 g (quantitative yield) of a clean mixture, consisting of quinazolinone **2a** and oxadiazole **5a**, in a ratio of 56:44, as determined by nmr (deuteriochloroform) integrals.

Rearrangement of 3,4-Dihydro-2,7-dimethyl-5*H*-1,3,4-benzotriazepin-5-one (**3b**) with *p*-Toluenesulfonic Acid.

A solution of 0.130 g (0.687 mmole) of **3b** in 20 ml of toluene containing a few mg of *p*-toluenesulfonic acid was heated at reflux for 90 minutes. The solution was concentrated and the residue was partitioned between chloroform and aqueous sodium bicarbonate solution. The organic phase was dried (sodium sulfate) and concentrated to leave 0.500 g (quantitative yield) of a clean mixture of hydrazide **2b** and oxadiazole **5b**, in a ratio of 78:22, respectively, as determined by nmr (deuteriochloroform) integrals.

2-Amino-5-nitrobenzoic Acid Hydrazide (**37**).

To 20.0 g (96.1 mmoles) of 5-nitroisatoic anhydride (Aldrich) in an open flask was added 75 ml of hydrazine hydrate. The addition was exothermic. After 16 hours of stirring, the mixture was diluted with water and the yellow solid was collected, washed with water and air-dried to give 16.6 g (88%) of **37**, mp 220-221° (lit [28] mp 206-210°, lit [32] mp 214-218°); ir (Nujol): 3400, 3340 and 3200 (broad) (NH and NH_2), 1640 ($\text{C}=\text{O}$), 1330 and 830 (NO_2) cm^{-1} ; nmr (dimethylsulfoxide- d_6): δ 8.38 (d, $J = 2.5$ Hz, 1H, H at 6-position), 7.98 (d of d, $J_{4,6} = 2.5$ Hz, $J_{4,3} = 9$ Hz, 1H, H at 4-position), 7.60 (broad s, 1H, NH), 6.77 (d, $J = 9$ Hz, 1H, H at 3-position), 3.50 (broad signal, 4H, both NH_2 groups).

Treatment of 2-Amino-5-nitrobenzoic Acid Hydrazide (**37**) with Four Equivalents of Triethyl Orthoacetate.

A mixture of 16.1 g (82.1 mmoles) of **37** and 53.2 g (0.328 mole) of triethyl orthoacetate was heated at reflux. After one hour, a clear solution resulted. After 16 hours, the solution was cooled in the refrigerator and the solid was collected and air-dried to yield 7.94 g (44%) of 3-amino-2-methyl-6-nitro-4(3*H*)-quinazolinone (**30**), mp 278-279° (dimethylformamide-ethanol); ir (Nujol): 3365, 3305 and 3185 (NH_2), 1645, 1610, 1585,

1540 (NO₂), 1335 (NO₂), 830 (NO₂) cm⁻¹; nmr (dimethylsulfoxide-d₆): δ 8.45 (d, J = 2.5 Hz, 1H, H at 5-position), 8.08 (d of d, J_{7,5} = 2.5 Hz, J_{7,8} = 9 Hz, 1H, H at 7-position), 7.89 (broad s, 2H, NH₂), 7.00 (d, J = 9 Hz, 1H, H at 8-position), 3.29 (s, 3H, CH₃), 2.61 (s, 3H, CH₃); ms: (70 eV, chemical ionization, methane) 221 (M⁺ + 1), 249 (M⁺ + 29), 261 (M⁺ + 41).

Anal. Calcd. for C₈H₈N₂O₃: C, 49.09; H, 3.66; N, 25.45. Found: C, 48.72; H, 3.35; N, 25.54.

A second crop of crystals from the filtrate above gave 2.40 g (11%) of 2-amino-5-nitrobenzoic acid (1-ethoxyethylidene)hydrazide (**40**), mp 174-175° (ethanol); ir (Nujol): 3355 and 3345 (NH₂), 3185 (NH), 1665 (sh), 1625, 1335 (NO₂), 830 (NO₂) cm⁻¹; nmr (dimethylsulfoxide-d₆): δ 10.52 (s, 1H, NH), 8.46 (d, J = 2.5 Hz, 1H, H at 6-position), 8.01 (d of d, J_{4,6} = 2.5 Hz, J_{4,3} = 9 Hz, 1H, H at 4-position), 7.52 (broad s, 2H, NH₂), 6.80 (d, J = 9 Hz, 1H, H at 3-position), 4.14 (q, J = 7.5 Hz, 2H, OCH₂), 2.95 (s, 3H, N=CCH₃), 1.25 (t, J = 7.5 Hz, 3H, CH₂CH₃); ms: (70 eV, chemical ionization, methane) 267 (M⁺ + 1), 295 (M⁺ + 29), 307 (M⁺ + 41).

Anal. Calcd. for C₁₁H₁₄N₄O₄: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.24; H, 5.23; N, 21.17.

The filtrate from above was concentrated to leave 4.57 g of material which was a mixture of components by tlc. This material was dissolved in ethanol and gravitationally filtered. During this process, more of **38** deposited on the filter paper. The filtrate deposited yellow needles, which were recrystallized from ethanol to give 450 mg (2%) of *N*-[2-methyl-5-nitro-4-oxo-3(4*H*)-quinazolinyl]ethanimidic acid (**39**), mp 147-148°; ir (Nujol): 1685 (C=O), 1515, 1345 and 865 (NO₂) cm⁻¹; nmr (dimethylsulfoxide-d₆): δ 8.79 (d, J = 2.5 Hz, 1H, H at 5-position), 8.50 (d of d, J_{7,5} = 2.5 Hz, J_{7,8} = 9 Hz, 1H, H at 7-position), 7.77 (d, J = 9 Hz, 1H, H at 8-position), 4.39 (q, J = 7.5 Hz, 2H, OCH₂), 2.47 (s, 3H, CH₃), 1.85 (s, 3H, CH₃), 1.37 (t, J = 7.5 Hz, 3H, CH₂CH₃); ms: (70 eV, chemical ionization, methane) 291 (M⁺ + 1), 319 (M⁺ + 29), 331 (M⁺ + 41).

Anal. Calcd. for C₁₃H₁₄N₄O₄: C, 53.79; H, 4.86; N, 19.30. Found: C, 53.69; H, 4.74; N, 19.41.

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