1,3,4-Benzotriazepinones. Formation and Rearrangement

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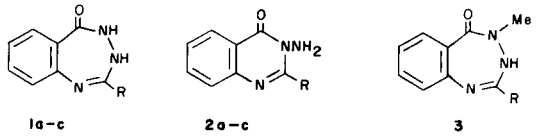
Received July 30, 1984

Anthranilic hydrazide reacts with orthoesters to produce mixtures of 3 products: 3,4-dihyro-5*H*-1,3,4-benzotriazepin-5-ones (**1**), 3-amino-3,4-dihydro-4-quinazolinones (**2**) and 2-(2-aminophenyl)-1,3,4-oxadiazoles (**4**). The origin of these materials has been investigated. Product distributions depend on the nature of substituents, solvent and time. In ethanol benzotriazepinones are kinetically favored, but formed reversibly they subsequently rearrange to **2** and **4**. Aminoquinazolinone formation is suppressed in aprotic solvents at moderate temperatures. Earlier failures to obtain **1** are due to its tendency to isomerize. Acid, base and thermal rearrangements have been observed. Mechanisms are proposed for the formation of **1, 2** and **4**, and for the rearrangements of the benzotriazepinones. Pyrazolo- and imidazotriazepinones have been prepared from the corresponding *o*-aminoazole hydrazides.

J. Heterocyclic Chem., **21**, 1817 (1984).

The therapeutic and commercial success of 1,4-benzodiazepines has stimulated considerable interest in related systems [1]. Among the numerous analogues prepared 3,4-dihydro-5*H*-benzotriazepin-5-one (**1a**) is notable for its absence. The compound has been described twice [2,3], but in each instance reinvestigation has shown the original reports to be incorrect [4,5]. Although the reported syntheses followed different routes, the actual product in both cases was the isomeric 3-amino-3,4-dihydro-4-quinazolinone (**2a**). Similarly, a product previously assigned as 2-phenyl-1,3,4-benzotriazepinone (**1c**) [6] has recently been shown to be 3-amino-2-phenyl-4-quinazolinone (**2c**) [7] and purported preparations of 2-(substituted-amino)-1,3,4-benzotriazepinones [8] have in fact proved to be isomeric 1,3,4-oxadiazoles (*cf*, **4**, below) [9]. Considerable confusion has thus surrounded the preparation of 1,3,4-benzotriazepinones.

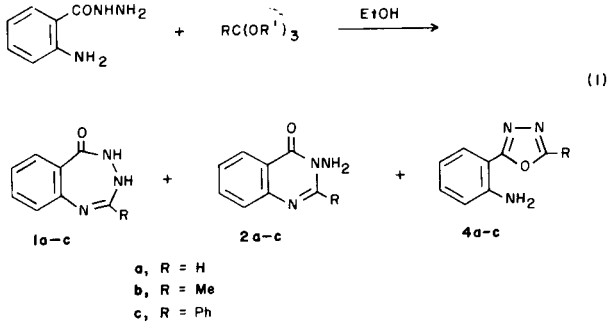


1a-c **2a-c** **3**

a, R = H
b, R = Me
c, R = Ph

Authentic benzotriazepinones (**1**) have recently been reported by Mérour (**1b** and related compounds) [10] and by Peet (**1c**) [7] *via* the reaction of anthranilic hydrazide and orthoesters. In addition to **1** varying amounts of 3-aminoquinazolinones **2** and 2-(2-aminophenyl)-1,3,4-oxadiazoles **4** [11] were also obtained. These product mixtures contrast with the uncontaminated 4-methyl-1,3,4-benzotriazepinones **3** produced by the analogous reaction of 1-(2-aminobenzoyl)-1-methylhydrazine (α-methylanthranilic hydrazide) with the orthoesters [12,13]. The present study was undertaken to explore the reasons for this difference and to account for earlier failures to obtain 4-unsubstituted benzotriazepinones **1**.

The reaction of anthranilic hydrazide and orthoesters was reexamined. As reported, excess refluxing triethyl orthoformate gave the *N*-ethoxymethylene derivative of **2a** [14] paralleling other examples of 3-amino-4-quinazolinone formation from anthranilic hydrazide [15]. But when the reaction was conducted with equivalent reactants in ethanol solution, two products in addition to **2a** were detected. Three products were similarly observed with triethyl orthoacetate and with trimethyl orthobenzoate. Isolation and characterization of the products from each of these reactions led to the assignments shown in equation 1.



(1)

1a-c **2a-c** **4a-c**

a, R = H
b, R = Me
c, R = Ph

Isomeric products **1, 2** and **4** are easily distinguished and identified. The fluorescent 2-(2-aminophenyl)-1,3,4-oxadiazoles **4a-c** display no carbonyl absorption in their ir spectra, while this absorption occurs between 1660-1700 cm^{-1} in **1** and **2**. Compounds **2a-c**, all previously reported, show a single deuterium oxide-exchangeable signal (2H, *ca.* δ 5.8, NH_2) in the ^1H nmr. The benzotriazepinones **1a-c** are yellow solids that exhibit two exchangeable sig-

nals (1H each, δ 8.2-10.0). The upfield signal is assigned to the N_3H and the downfield to the N_4H, in analogy with related compounds [13].

With pure samples in hand quantitative analysis of products formed under various conditions was possible. Since no additional materials were found, unpurified reaction mixtures were conveniently analyzed by nmr with peak assignments made by reference to the authentic compounds. Determinations on known mixtures showed the method accurate to ±4%.

Product distributions are affected by both substituent R and the duration of reaction (Table I). Prolonged reaction afforded greater amounts of oxadiazole **4** and correspondingly less aminoquinazolinone **2** as the bulk of R increased, in effect also noted in 1-butanol. Regardless of R, yields of benzotriazepinone **1** were found to be strikingly time dependent. Although appreciable quantities are present at short reaction times, prolonged reaction eliminates

Table I

Products: Anthranilic Hydrazide and Orthoesters in Refluxing Ethanol [a]

R	Time, hours	Products, % [b] 1	2	4
H	211	—	100	—
	0.3 [c]	36	54	10
Me	211	—	45	55
	5	51	19	29
Ph	220	5	8	87
	5	57	8	35

[a] See eq 1. Reactants 0.500*M*. [b] ± 4%. [c] One drop acetic acid added.

or greatly diminishes benzotriazepinone formation. A clearer picture of the time dependence emerged by following product concentrations as a function of time in the reaction of anthranilic hydrazide and triethyl orthoacetate (Figure 1). Under the conditions employed reactants disappeared within 5 hours and neither additional products nor transients were detected (tlc, nmr).

Figure 1 reveals benzotriazepinone **1b** to be kinetically favored product, but its formation is clearly reversible. Rising rapidly to a maximum, the benzotriazepinone concentration subsequently decreases as it rearranges to **2b** and **4b**. Isomerization of **1** to **2** and **4** in refluxing ethanol was independently verified starting from pure samples of **1a-c**.

As opposed to hydroxylic solvents, the benzotriazepinones are indefinitely stable in aprotic media at temperatures below 120°. Accordingly, the formation of benzotriazepinones under irreversible conditions *ie*, nonhydroxylic solvents was investigated. In a series of such solvents the

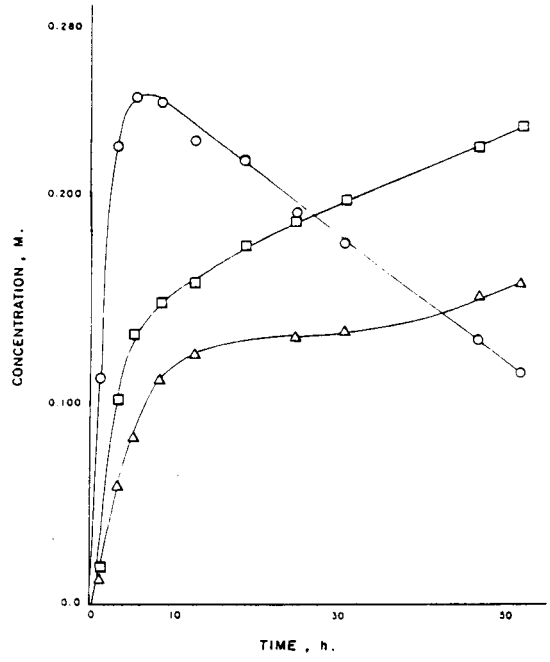


Figure 1. Concentration *vs.* time profile for the reaction of anthranilic hydrazide and triethyl orthoacetate, 0.500 *M* in ethanol. Products: **1b**, O; **2b** △; **4b**, □.

reaction proceeded smoothly producing only **1** and **4**; aminoquinazolinone formation was completely supressed (Table II). Furthermore, the ratio of **1** to **4** increased dramatically with solvent polarity [16], an effect of both mechanistic and preparative significance.

Table II

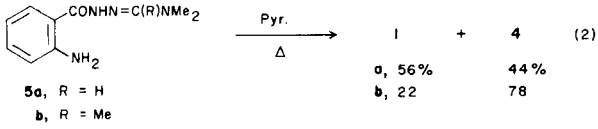
Anthranilic Hydrazide and Triethyl Orthoacetate in Nonhydroxylic Solvents [a]

Solvent	Products, % **1b**	**4b**
Benzene	5	95
Pyridine	33	66
DMF, 100°	55	45

[a] Reactants 0.200 *M*. Reaction time 26-42 hours.

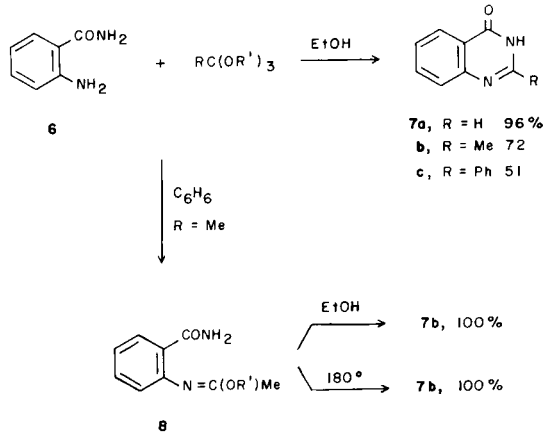
Analogous exclusion of aminoquinazolinones was also observed in the aprotic cyclizations of **5**. These compounds, obtained by condensation of anthranilic hydrazide with *N,N*-dimethylformamide and *N,N*-dimethylacet-

amide dimethyl acetals, afforded only **1** and **4** in aprotic solvents, whereas **1**, **2** and **4** were formed in ethanol. Results with pyridine solvent are shown in equation 2.



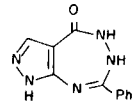
Aminoquinazolinones **2** have previously been prepared from anthranilic hydrazide and various acylating agents [15b] in a reaction formally similar to the venerable Niementowsky synthesis of 4-quinazolinones [17]. However, the reported preparations of 3-aminoquinazolinones (as well as the numerous and diverse Niementowsky-type reactions) have generally been conducted at elevated temperatures, conditions more rigorous than those of the present study. To determined the feasibility of cyclization in this manner under our conditions, anthranilamide (**6**) was reacted with orthoesters in ethanol solution. Cyclization to the 4-quinazolinones **7a-c** occurred readily with the indicated isolated yields (Scheme 1). In benzene, on the other

Scheme I

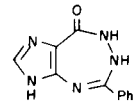


hand, triethyl orthoacetate produced **8**, the probable intermediate in the formation of **7**. On heating in ethanol, or at 180°, **8** quantitively cyclized to **7b**. Thus Niementowsky-type cyclization is indeed possible and probable under our conditions. The isolation of **8** suggests a similar intermediate as the precursor of the 3-aminoquinazolinones **2**. Additionally, these results provide evidence concerning the course of this general but little studied cyclization process [17,18].

The reaction of anthranilic hydrazide and orthoesters is a synthetically versatile process. By modification of conditions the reaction may be selectively directed toward products **1**, **2** or **4**. Non-polar solvents favor oxadiazole **4** formation, while hydroxylic solvents and acid catalysis maximize the aminoquinazolinones **22**. Benzotriazepinones **1** can be obtained in either hydroxylic or aprotic solvents. Although the former is limited by the instability of **1**, satisfactory yields (see Experimental) were achieved with tlc monitoring and early work-up procedures. Nonhydroxylic solvents offer the advantage of fewer products and irreversible formation of **1** [19]. Extension of these methods allowed preparation of the pyrazolo- **9** and imidazotriazepinones **10**.



9



10

The isomerization of **1** in ethanol but not aprotic solvents suggest an acid-catalyzed rearrangement, a process recently observed by Peet and Sunder [11]. Treated with catalytic quantities of strong acid, benzotriazepinones **1a-c** were found to rearrange rapidly to mixtures of the corresponding aminoquinazolinones **2** and oxadiazoles **3**. Typical data for the acid-catalyzed rearrangement of **1b** are given in Table III. Following disappearance of **1b** a slower secondary rearrangement of the oxadiazole **4b** to the aminoquinazolinone **2b** was also observed. This process was verified by subjecting pure **4b** to the indicated acidic conditions. Isomerization of oxadiazole **4a** to **2a** has previously been effected with formic acid [14].

Table III

Acid-Catalyzed Rearrangement of **1b** [a]

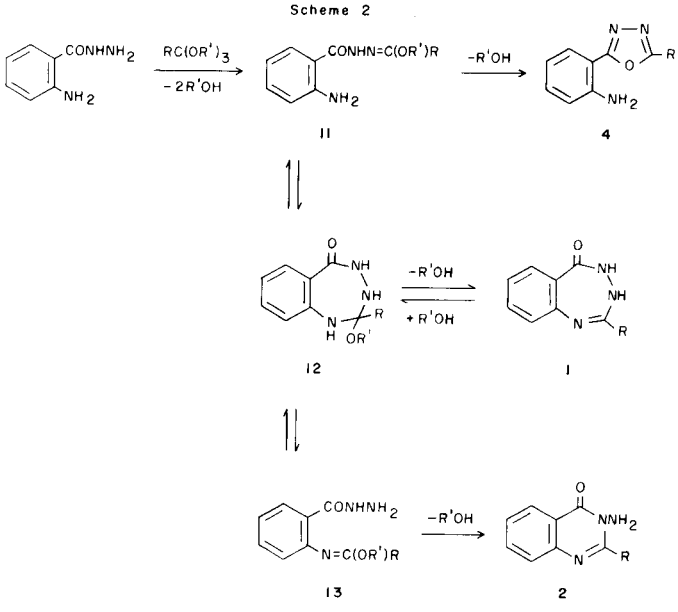
Time, hours	Products, % 1b	2b	4b
0	100	—	—
0.25	7	71	21
2	6	73	20
50	—	78	21
144	—	83	17
280	—	100	—

[a] Refluxing ethanol. Initial concentration, 0.200 *M*; H^+ = 0.012 *M* (hydrochloric acid).

A base-induced rearrangement of 4-methyl-1,3,4-benzotriazepin-5-ones **3** has been reported by Leiby and Heindel [20]. The same process appears to occur when **1a-c** are treated with catalytic quantities of sodium ethoxide in ethanol solution. In accord with the proposed mechanism [20], aminoquinazolinones **2a-c** were the exclusive, quantitative products. The corresponding oxadiazoles are stable under the basic conditions employed and thus are not involved in these rearrangements. It is noteworthy that hydrazine hydrate also effects the base-catalyzed isomerization of **1**. One of the earlier erroneous reports of **1a** describes its preparation by means of this reagent [3]. While the product may have formed transiently, it is clear that **1a** would not survive the reported conditions [5].

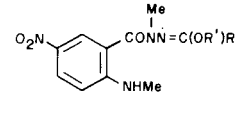
At its melting point benzotriazepinone **1a** irreversibly loses its bright yellow color. Investigation of this phenomenon revealed a third mode of rearrangement, thermal isomerization. Similar to the acid-catalyzed reaction, thermolysis produces mixtures of **2** and **4**, although product ratios are markedly different. A sample of **1b** maintained at 180-190°, for example, completely rearranged to **2b** (30%) and **4b** (70%) after 5 hours. The products **2b** and **4b** were shown to be stable at this temperature. Thermolysis was also observed in refluxing diglyme and orthoester solvents. The pyrolytic isomerization of **1a-c** contrasts with the apparent stability of the 4-methylbenzotriazepinones **3**. The latter were prepared in refluxing solutions of high boiling orthoesters [13].

Scheme 2

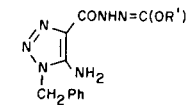


The reaction of anthranilic hydrazide and orthoesters provides an interesting example of competitive cyclization to 5-, 6- and 7-membered ring products, **4**, **2** and **1**, respectively. A pathway consistent with the results and supported by additional information is shown in Scheme 2.

Initial condensation would be expected to occur at the most nucleophilic site, the terminal hydrazido nitrogen, producing intermediate **11**. Direct evidence for **11** (also **12** and **13**) was sought but not obtained in the present study. However, more stable analogues *eg* **5** have been isolated elsewhere. Leiby and Heindel succeeded in intercepting **14**, but only when a deactivating *p*-nitro substituent was present [13]. The 5-amino group of 4-acyl-1,2,3-triazoles is notably non-nucleophilic [21] and nonbasic [22]. Accordingly, 5-amino-1-benzyl-1,2,3-triazole-4-carboxylic acid hydrazide condensed with orthoesters to give the stable products **15a-c**. Our failure to detect **11** (Scheme 2) suggests rapid nucleophilic involvement of the *o*-amino group with consequent formation of intermediate **12**.



14 R = Me, Ph



15a, R = H
b, R = Me
c, R = Ph

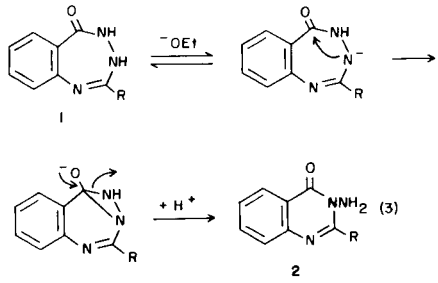
Formation of 2-(2-aminophenyl)-1,3,4-oxadiazoles **4** is not surprising since 2-aryl-5-substituted-1,3,4-oxadiazoles have been prepared by refluxing aryl hydrazides with orthoesters [23]. More recently, Peet obtained **4b** (as well as **1b** and **2b**) [11] under conditions essentially identical to those of our study. The observed enhancement of benzotriazepinone at the expense of oxadiazole as nonhydroxylic solvent polarity increased (Table III) may well reflect the more polar nature of reactions leading to **1** as opposed to **4**.

Hydrolysis and methoxyaminolysis of cyclic amidines, including the closely related 4,5-dihydro-3*H*-1,3-benzodiazepine, have been investigated by Burdick, Benkovic and Benkovic [24]. The behavior of tetrahedral intermediates analogous to **12** was interpreted in terms of the stereoelectronic principles proposed by Lehn and Deslongchamps [25]. Applied to **12** the analysis substantiates the observed reversible elimination of R'OH, presumably from a chair-like conformation. Interconversion to the boat conformation, an energetically feasible process, would allow ejection of either the aniline or hydrazide nitrogens, affording **11** and **13** respectively. The depicted fate of intermediate **12** therefore accords with theory and results obtained in related systems.

The isolation of **8** (from anthranilamide) and the demonstration of its facile cyclization in ethanol solution (Scheme 1) strongly supports intermediate **13** as the precursor of the aminoquinazolinones **2**. The dramatic effect of aprotic solvents in inhibiting formation of **2** (Table II) appears to be associated with the cyclization mechanism (**13** → **2**), although solvent supression of **13** cannot as yet be ruled out.

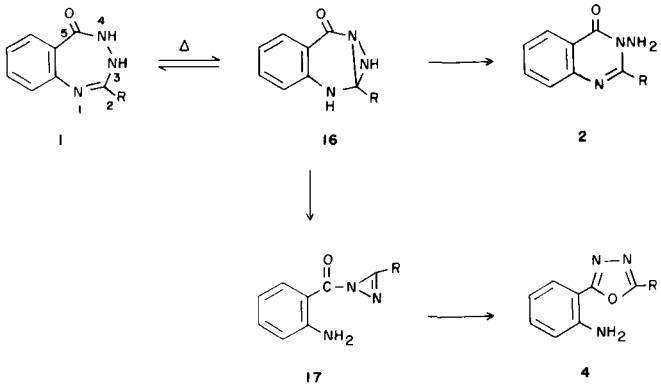
The acid-catalyzed rearrangement of benzotriazepinones (Table III) is well accomodated by Scheme 1. Acid-induced ethanolysis of the amidine function of **1** would afford intermediate **12**, and ultimately the observed products, **2** and **4**. A similar mechanism has been postulated elsewhere [11].

Exclusive formation of aminoquinazolinones **2** in the base-catalyzed rearrangement argues against **12** in this process. Proton abstraction from the amidine, on the other hand, could initiate a pathway leading only to **2**, as previously proposed for the 4-methylbenzotriazepinones (equation 3) [20].



Models of **1** reveal the proximity of C_2 and N_4. Thermolytic rearrangement of benzotriazepinones might thus result from transannular interaction of these centers *via* internal Niementowsky-type reaction, entirely analogous to the thermal cyclization of **8** (Scheme 1). Although the mechanism of this reaction, and indeed the many related cyclizations [17], remains to be elucidated [26], ring-closure in this manner would presumably afford the diaziridine intermediate **16** (Scheme 3). Rupture of the diaziridine ring with H migration from N_1 to N_3 (benzotriazepinone numbering retained) would give the aminoquinazolinone **2**.

Scheme 3



H Migration in the opposite sense (N_3 to N_1) with cleavage of the N_1-C_2 bond would produce the 1-acyl-1*H*-diazirine **17**. As with similar systems [27], **17** would be expected to undergo thermal ring-expansion to **4**. The isomeric 5-(2-aminophenyl)-3-methyl-1,2,4-oxadiazole, product of ring-expansion *via* cleavage of the N-N bond of **17** (from **1b**), was independently synthesized [28] and shown to be absent from the thermolytic product mixture. The greater thermal stability of 4-methylbenzotriazepinones **3** in comparison with **1a-c** would appear due to the inability of **3** to form an intermediate comparable to **17**.

Benzotriazepinones **1a-c** emerge from this study as a remarkably sensitive system, capable of undergoing acid, base and thermally induced rearrangements, each *via* distinctly different paths. It is thus apparent why previous attempts to prepare **1a** under acidic [2] or basic [3] conditions were unsuccessful.

EXPERIMENTAL

The ir spectra were recorded as mulls or films on a Perkin-Elmer 457 spectrophotometer. The nmr spectra were recorded in DMSO-d_6 (TMS added) on a Varian EM-360 spectrophotometer. The tlc analysis was performed with Eastman 13181 silica gel sheets using 10% methanol in chloroform or ethyl acetate as eluents. Uncorrected capillary melting points were determined with an Electrothermal apparatus. Elemental analyses were performed by Atlantic Microlab, Inc., Atlantic, GA.

3,4-Dihydro-5*H*-1,3,4-benzotriazepin-5-one (**1a**).

A solution of anthranilic hydrazide (1.51 g, 10.0 mmoles), triethyl orthoformate (1.56 g, 10.5 mmoles) and 20 ml of DMF was refluxed 1 hour. The warm bright yellow solution was diluted with 40 ml of benzene and refrigerated overnight. A white precipitate (0.12 g) was filtered and discarded, and the filtrate was evaporated under reduced pressure. The residue taken up in 100 ml of acetone deposited in two crops 0.66 g (41%) of yellow crystals, mp 200-207°. Two recrystallizations from acetone gave the analytical sample, mp 209-210°; nmr: δ 9.57 (s, 1H, deuterium oxide exch, N_4H), 8.48 (s, broad, 1H, exch, N_3H), 7.73 (m, 1H, *ortho* to C=O), 7.33 (m, 1H, *para* to C=O), 6.63-6.97 (m, 3H, 2 ArH, C_2H); ir: 3263, 3195 (NH_2), 1670 (C=O) cm^{-1}.

Anal. Calcd. for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.68; H, 4.41; N, 26.06.

3,4-Dihydro-2-methyl-5*H*-1,3,4-benzotriazepin-5-one (**1b**).

A solution of anthranilic hydrazide (13.02 g, 20.0 mmoles) and triethyl orthoacetate (3.56 g, 21.3 mmoles) in 40 ml of absolute ethanol was refluxed 1.5 hours, then concentrated by boiling to 10-15 ml. Hot benzene (200 ml) was added and crystallization occurred on cooling to room temperature. After overnight refrigeration the yellow crystals were collected and dried, yield, 1.68 g (48%), mp 198-200°. Two recrystallizations from benzene-ethyl acetate gave the analytical sample, mp 206-207° reported mp 205° [10], 200-202° [11]; nmr: δ 9.50 (s, 1H, deuterium oxide exch, N_4H), 8.22 (s, 1H, deuterium oxide exch, N_3H), 7.68 (m, 1H, *ortho* to C=O), 7.33 (m, 1H, *para* to C=O), 6.68-7.02 (m, 2H, aromatic), 1.93 (s, 3H, CH_3); ir: 3265, 3200 (NH), 1683 (C=O) cm^{-1}.

Anal. Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.86; H, 5.23; N, 23.91.

3,4-Dihydro-2-phenyl-5*H*-1,3,4-benzotriazepin-5-one (**1c**).

A solution of anthranilic hydrazide (3.00 g, 16.46 mmoles) and trimethyl orthobenzoate (2.00 g, 13.23 mmoles) in 30 ml of absolute ethanol was refluxed 4 hours and 15 minutes. The yellow suspension was evaporated (0.3 mm, 60°) and the residue crystallized from 300 ml of absolute ethanol, yield, 1.45 g (46%), mp 268-269°. Two recrystallizations from ethanol gave the analytical sample, mp 269-269.5°, reported 256-257° [7]; nmr: δ 10.02 (s, 1H, deuterium oxide exch, N_4H), 8.68 (s, 1H, deuterium oxide exch, N_3H), 6.83-7.83 (m, 9H, aromatics); ir: 3300, 3185 (NH), 1660 (C=O) cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found; C, 70.88; H, 4.69; N, 17.67.

5,6-Dihydro-7-phenyl-4*H*-pyrazolo[3,4-*e*]-1,2,4-triazepin-4-one (**9**).

A mixture of 3-amino-4-pyrazolecarboxylic acid hydrazide [29] (2.82 g, 20.0 mmoles), trimethyl orthobenzoate (4.00 g, 22.0 mmoles), 1.0 ml of glacial acetic acid and 40 ml of methanol was refluxed 1.5 hours. The warm yellow suspension was filtered affording 0.59 g of crude product, mp 237-243°. Analysis (tlc) showed this material to be **9** slightly contaminated with 3-amino-4-pyrazolecarboxylic acid hydrazide. The filtrate deposited in 3 crops an additional 1.01 g of **9**, mp 281-285°, total crude yield, 1.60 g (35%). Three recrystallizations from acetone gave the analytical sample, mp 293.5-295°; nmr: δ 12.67 (s, broad, 1H, deuterium oxide exch, pyrazole NH), 9.37 (s, 1H, deuterium oxide exch, N_5H), 9.22 (s, 1H, deuterium oxide exch, N_6H), 7.95 (s, 1H, C_3H), 7.30-7.75 (m, 5H, aromatics); ir: 3320, 3218 (NH), 1670 (C=O) cm^{-1}.

Anal. Calcd. for $C_{11}H_9N_5O$: C, 58.14; H, 3.99; N, 30.82. Found: C, 57.98; H, 4.01; N, 30.72.

5-Amino-4-imidazolecarboxylic Acid Hydrazide.

A suspension of 5-amino-4-carbethoxyimidazole [30] (1.30 g, 8.40 mmoles) and 4.0 ml of hydrazine hydrate was stirred at room temperature. After 3 days a pale yellow solution was obtained. The product crystallized after another day and was collected and washed with small amounts of ethanol, yield, 1.12 g (94%), mp 193-196° dec. Two recrystallizations from ethanol gave the analytical sample, mp 201-203° dec; nmr: δ *ca.* 13.0 (1H, v broad, deuterium oxide exch, imidazole NH), 8.42 (s, 1H, deuterium oxide exch, amido H), 7.08 (s, 1H, imidazole CH), 5.43 (4H, broad, deuterium oxide exch, NH_2).

Anal. Calcd. for $C_4H_7N_5O$: C, 34.04; H, 5.00; N, 49.62. Found: C, 33.96; H, 5.01; N, 49.53.

5,6-Dihydro-7-phenyl-4*H*-imidazo[4,5-*e*]-1,2,4-triazepin-4-one (**10**).

A mixture of 5-amino-4-imidazolecarboxylic acid hydrazide (1.28 g, 9.10 mmoles), trimethyl orthobenzoate (1.82 g, 10.0 mmoles) and 18 ml of ethanol was refluxed for 22 hours. The resulting yellow suspension was cooled and filtered, yield, 1.54 g (74%, crude), mp 233-236°; tlc indicated mainly **10**. Three crystallizations from ethanol gave the analytical sample, mp 262-263°; nmr: δ *ca.* 12.7 (1H, v broad, dueterium oxide exch, NH), 9.23 (s, 1H, NH), 9.10 (s, 1H, NH), 7.55 (s, imidazole CH), 7.27-7.77 (m, 6H, ArH's and imidazole CH); ir: 3300, 3208 (NH), 1668 (C=O) cm^{-1}.

Anal. Calcd. for $C_{11}H_9N_5O$: C, 58.15; H, 3.99; N, 30.82. Found; C, 58.06; H, 3.98; N, 30.79.

3-Amino-3,4-dihydro-4-quinazolinone (**2a**).

This compound was prepared in 86% yield by refluxing anthranilic hydrazide (3.02 g, 20.0 mmoles) and triethylorthoformate (3.11 g, 21.0 mmoles) in 50 ml of absolute ethanol for 2 hours. The crystallized product, 2.76 g, mp 206-209°, was recrystallized from 75 ml of ethanol, mp 210-211°, reported mp 209-210° [32]; nmr: δ 8.25 (s, 1H, C_2H), 8.05 (m, 1H, *ortho* to C=O), 7.20-7.83 (m, 3H, ArH), 5.75 (s, 2H, deuterium oxide exch, NH_2); ir: 3280, 3158 (NH_2), 1680 (C=O) cm^{-1}.

3-Amino-3,4-dihydro-2-methyl-4-quinazolinone (**2b**).

A solution of anthranilic hydrazide (1.51 g, 10.0 mmoles), triethyl orthoacetate (1.78 g, 11.0 mmoles), 1 drop of 12 *M* hydrochloric acid and 20 ml of ethanol was refluxed 48 hours, then evaporated to a tan solid. Crystallization from 75 ml of benzene gave in two crops, crude product, 1.40 g (80%), mp 121-130°, while recrystallized from ethanol gave, gave **2b**, 0.65 g, mp 149-150°, reported mp 149.5° [33], 147-148° [31]; nmr: δ 8.13 (m, 1H, *ortho* to C=O), 7.33-7.93 (m, 3H, ArH), 5.82 (s, 2H, deuterium oxide exch, NH_2), 2.60 (s, 3H, CH_3); ir: 3200 (NH_2), 1663 (C=O) cm^{-1}.

3-Amino-3,4-dihydro-2-phenyl-4-quinazolinone (**2c**).

A solution of anthranilic hydrazide (2.00 g, 13.2 mmoles), trimethyl orthobenzoate (13.00 g, 16.5 mmoles) and 30 ml of ethanol was refluxed 15 hours, cooled to room temperature and filtered. On cooling overnight the filtrate deposited 0.54 g (17%) of crude **2c**, mp 153-160°. Recrystallization (ethanol) gave product, mp 182-183°, identical with sample prepared from anthranil [34]; nmr: δ 7.48-8.45 (m, 9H, ArH), 5.68 (s, 2H, deuterium oxide exch, NH_2); ir: 3299, 3205 (NH_2), 1658 (C=O) cm^{-1}.

2-(2-Aminophenyl)-1,3,4-oxadiazole (**4a**).

A solution of anthranilic hydrazide (1.51 g, 10.0 mmoles), triethyl orthoformate (1.56 g, 10.5 mmoles) and 10 ml of diglyme was refluxed 48 hours, then evaporated to dryness under reduced pressure. The solid residue was boiled with five 25-ml portions of hexane and the supernatants filtered. The combined hexane extracts were evaporated to give 0.14 g (9%), mp 67-70°. Recrystallization from hexane gave **4a**, mp 72-74°, identical to an authentic sample prepared by the method of Vincent [14]; nmr: δ 9.27 (s, 1H, oxadiazole H), 6.60-7.80 (m, 6H, ArH and NH_2), 6.82 (s, exch, NH_2); ir: 3421, 3338 (NH_2), 1620 (C=N) cm^{-1}.

2-(2-Aminophenyl)-5-methyl-1,3,4-oxadiazole (**4b**).

A solution of anthranilic hydrazide (1.51 g, 10.0 mmoles) and triethyl orthoacetate (1.78 g, 11.0 mmoles) in 20 ml of diglyme was refluxed 49 hours, then evaporated to a pale yellow powder. Crystallization from 50 ml of aqueous ethanol (2:1) gave 1.25 g (71%), mp 148-149°. Two recrystallizations gave white needles, mp 151-152°; reported, 149-150° [11]; nmr: δ 6.5-7.7 (m, 6H, ArH and NH_2), 2.55 (s, 3H, CH_3); ir: 3442, 3397, 3340, 3300 (NH_2), 1617 (C=N) cm^{-1}.

Anal. Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.66; H, 5.18; N, 23.98.

2-(2-Aminophenyl)-5-phenyl-1,3,4-oxadiazole (**4c**).

A solution of anthranilic hydrazide (0.76 g, 5.2 mmoles) and trimethyl orthobenzoate (0.96 g, 5.3 mmoles) in 10 ml of anhydrous 1,4-dioxane was refluxed 7 hours. Analysis (tlc) showed only **4c** and traces of anthranilic hydrazide. The solution was evaporated and recrystallized from ethanol, yield 0.83 g (70%), mp 166-167°. Two recrystallizations (ethanol) gave the analytical sample, mp 167-167.5°, reported mp 167-168° [7]; nmr: δ 6.57-8.20 (m, ArH), 6.80 (s, deuterium oxide exch, NH_2); ir: 3415, 3315 (NH_2), 1602 (C=N) cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.61. Found: C, 70.67; H, 4.72; N, 17.64.

1-(2-Aminobenzoyl)-2-dimethylaminomethylene Hydrazine (**5a**).

A solution of anthranilic hydrazide (1.51 g, 10.0 mmoles), 1.85 ml (*ca.* 12.9 mmoles) *N,N*-dimethylformamide dimethyl acetal and 45 ml of benzene was heated to reflux and the solvent distilled slowly (2 hours) from the mixture. A white precipitate appeared after 10 minutes. After 40 ml of benzene had distilled the resulting paste was diluted with 30 ml of ether and the solid collected, 1.77 g (86%), mp 155-160°. Two recrystallizations from ethanol-ethyl acetate (2:1) gave **5a**, mp 170-173°.

Anal. Calcd. for $C_{10}H_{14}N_4O$: C, 58.24; H, 6.84; N, 27.16. Found: C, 58.16; H, 6.88; N, 27.15.

1-(2-Aminobenzoyl)-2-(1-dimethylaminoethylidene)hydrazine (**5b**).

This compound was prepared as for **5a** from anthranilic hydrazide and *N,N*-dimethylacetamide dimethyl acetal, 79%, mp 173-174° dec.

Anal. Calcd. for $C_{11}H_{16}N_4O$: C, 59.98; H, 7.32; N, 25.43. Found: C, 60.08; H, 7.33; N, 25.44.

4,5-Dihydro-4-quinazolinone (**7a**).

A solution of anthranilamide (1.36 g, 10.0 mmoles), triethyl orthoformate (1.63 g, 11.0 mmoles) and 20 ml of ethanol was refluxed 43 hours, cooled and the crystallized product collected, yield 2.20 g (96%), mp 221-222°. There was no depression of mixed mp with a purified authentic sample (Aldrich), and the nmr and ir were identical to the authentic material.

4,5-Dihydro-2-methyl-4-quinazolinone (**7b**).

This compound was prepared as described for **7a**, 72% yield, mp 232-233°, reported mp 232° [35].

4,5-Dihydro-2-phenyl-4-quinazolinone (**7c**).

This compound was prepared as described for **7a**, 51% yield, mp 242-243°, reported mp 235-236° [36].

2-(1-Ethoxyethylidenamino)benzamide (**8**).

A solution of anthranilamide (1.36 g, 10.0 mmoles) and triethyl orthoacetate (1.87 g, 10.5 mmoles) in 20 ml of benzene was refluxed 4.5 hours and the solvent removed under reduced pressure. The residue was recrystallized from 15 ml cyclohexane to give 0.94 g (45%), mp 110-112°. Two additional recrystallizations gave the analytical sample, mp 114-117°; nmr: δ 6.68-7.80 (m, 6H, ArH and NH_2 exch, 2H *ca.* 7.4, NH_2), 4.23 (q, 2H, OCH_2), 1.82 (s, 3H, CH_3), 1.32 (t, 3H, CH_2CH_3); ir: 3372, 3142 (NH_2), 1658 (C=O), 1640 (C=N) cm^{-1}.

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.02; H, 6.85; N, 13.57.

5-Amino-1-benzyl-1,2,3-triazole-4-carboxylic Acid (2-*N*-Ethoxymethylene)hydrazide (**15a**).

A mixture of 5-amino-1-benzyl-1,2,3-triazole-4-carboxylic acid hydrazide [37], (1.00 g, 4.30 mmoles), triethyl orthoformate (8.91 g, 60.1 mmoles) and 100 ml of ethanol was refluxed for 2 hours, then evaporated under reduced presure (0.3 mm, 80°). The residue was recrystallized from 50 ml of benzene to afford 0.78 g (63%), mp 122-130°. Two additional recrystallizations gave the analytical sample, mp 131-133°; nmr: δ 9.73 (s, 1H, deuterium oxide exch, amido NH), 7.28 (s, 5H, ArH), 7.03 (s, 1H, imino CH), 6.55 (s, 2H, deuterium oxide exch, NH_2), 5.48 (s, 2H, benzyl CH), 4.25 (q, 2H, ethoxy CH_2), 1.32 (t, 3H, ethoxy CH_3).

Anal. Calcd. for $C_{13}H_{16}N_6O_2$: C, 54.16; H, 5.59; N, 29.15. Found: C, 54.10; H, 5.61; N, 29.12.

5-Amino-1-benzyl-1,2,3-triazole-4-carboxylic Acid (2-*N*-1'-Ethoxyethylidene)hydrazide (**15b**).

5-Amino-1-benzyl-1,2,3-triazole-4-carboxylic acid hydrazide (2.00 g, 8.61 mmoles) and 25 ml of triethyl orthoacetate were refluxed for 17 hours. The resulting suspension was cooled and the white crystalline product was collected, yield, 1.42 g (55%), mp 182-185°. Recrystallizations from ethanol, then ethyl acetate gave the analytical sample, mp 180-183°. This material is a 1:2.2 mixture of *syn* and *anti* isomers, as determined from the CH_3 peak heights and the ratio of amido hydrogens; nmr (deuteriochloroform): δ 9.75, 8.63 (two singlets, 1H, deuterium oxide exch, amido H), 7.18 (s, 5H, ArH), 5.28 (s, 2H, benzyl CH_2), 4.98 (s, 2H, deuterium oxide exch, NH_2), 4.10 (m, 2H, ethoxy CH_2), 2.08 and 2.02 (two singlets, 3H, imino CH_3), 1.30 (m, 3H, ethoxy CH_3).

Anal. Calcd. for $C_{14}H_{18}N_6O_2$: C, 55.60; H, 6.00; N, 27.80. Found: C, 55.55; H, 6.02; N, 27.74.

5-Amino-1-benzyl-1,2,3-triazole-4-carboxylic Acid (2-*N*-1'-Methoxybenzylidene)hydrazide (**15c**).

A suspension of 5-amino-1-benzyl-1,2,3-triazole-4-carboxylic acid hydrazide (2.00 g, 8.61 mmoles), trimethyl orthobenzoate (1.57 g, 8.61 mmoles) and 20 ml of methanol was refluxed 117 hours, cooled and filtered, yield, 2.02 g (67%), mp 188-194°. After 2 recrystallizations, (methanol), mp 196-198°. This material is a 1:3 mixture of *syn* and *anti* isomers as determined from the CH_3 peak heights and the ratio of amide hydrogens; nmr: δ 10.03, 9.58 (two singlets, 1H, deuterium oxide exch, amido H), 7.00-7.62 (m, 10H, ArH), 6.48, 6.33 (two singlets, broad, 2H, deuterium oxide exch, NH_2), 5.40, 5.33 (two singlets, 2H, benzyl H), 3.85, 3.78 (two singlets, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{18}N_6O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.63; H, 5.25; N, 23.97.

Product Analysis of the Reaction of Anthranilic Hydrazide and Triethyl Orthoacetate (Figure 1).

To a hot solution of 0.1285 mole of triethyl orthoacetate in 250 ml of absolute ethanol was added 0.1250 mole anthranilic hydrazide. The solution was refluxed and 1.00 ml samples were periodically withdrawn by syringe through a serum-capped neck. Analysis (tlc) of the samples showed only **1b, 2b** and **4b**, as well as anthranilic hydrazide in the early stages of reaction. Solvent and unreacted triethyl orthoacetate were removed under reduced pressure (0.2 mm, 50°) and the residues in DMSO-d_6 were examined by nmr. Concentrations of products were calculated from the peak heights of the methyl signals and the total moles present, after correction for unreacted anthranilic hydrazide and for volume changes due to sampling.

Acid-Catalyzed Rearrangement of **1**.

Solutions containing 1.00 mmole of **1** and 0.060 mole of hydrochloric acid in 5.00 ml of ethanol were refluxed and followed by tlc. Quantitative analyses (see Table III) were conducted at 10 times the above scale. Samples (1.00 ml) were withdrawn, solvent removed under reduced pressure, and the nmr (DMSO-d_6) of the residue determined. After 50 hours **1a** was converted to **2a** (100%); **1c** was converted to **2c** (67%) and **4c** (33%).

Base-Catalyzed Rearrangement of **1**.

Solutions containing 1.000 mole of **1** and 0.050 moles of sodium ethoxide in 5.00 ml of absolute ethanol were refluxed and monitored by tlc. All rearrangements were complete within 5 hours and produced only the corresponding 3-aminoquinazolinones. Removal of solvent and recrystallization gave pure samples of **2a-c**. Oxadiazoles **4a-c** were unaffected by 10 hours reflux under these conditions. Solutions of **1** (1.00 mmole) with 1.00 g of hydrazine hydrate and 5.0 ml of ethanol rearranged to **2** on refluxing 4-6 hours.

Thermolysis of **1**.

Samples of **1** (0.30 g) were heated 5-10 hours by means of an oil bath; **1a,b** (180-190°), **1c** (250-260°). Analysis (tlc) of the resulting products showed mixtures of **2** and **4**, as well as traces of starting material with **1c**. Quantitative analysis of the products from **1b** used the nmr methyl peak heights and showed **2b** (30%) and **4b** (70%).

Acknowledgement.

We thank the NIH-Minorities Biomedical Support Program for support of this research, Grant No. RR08153-07.

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