The Chemistry of 2-Aminobenzoyl Hydrazides. 1. Effects of Orthoester Substituents on the Mode of Cyclization [1]

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Received July 30, 1984

Treatment of substituted 2-aminobenzoyl hydrazides with orthoesters has been found to yield different products depending upon the type of orthoester employed. Equimolar quantities of orthoester and hydrazide yield 3-amino-4(3*H*)-quinazolinones, whereas utilization of a two-fold excess (or greater) of orthoester yields, in some cases, 3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones as minor products in addition to *N*-[4(3*H*)-quinazolinon-3-yl]imidate esters as major products. Treatment of hydrazides with trimethyl orthobenzoate yields substituted 5-(2-aminophenyl)-1,3,4-oxadiazoles and 3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones. The steric bulk of the phenyl group in trimethyl orthobenzoate effects the formation of adduct at the β-nitrogen of the hydrazide which cyclized to the oxadiazole and benzotriazepinone products. In the aliphatic orthoester series, the formation of adduct to the aromatic amino group appears to be favored which gives rise to quinazolinone and benzotriazepinone products.

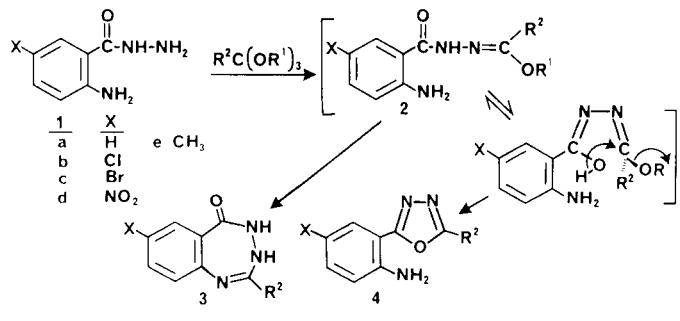
J. Heterocyclic Chem., **21**, 1825 (1984).

Stimulated by the vast amount of research in the benzodiazepine class of medicinal agents, more recent research efforts have also been directed towards the synthesis of benzotriazepines [2]. The present paper details the attempted synthesis of substituted 3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones **3**, 1,3,4-oxadiazoles **4**, and *N*-[4(3*H*)-quinazolinon-3-yl]imidate esters **6** by the condensation of orthoesters with 5-substituted-2-aminobenzoyl hydrazides. Earlier approaches claimed the preparation of 3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-one through hydrazine and anthranilate ester adducts of ethoxymethylene malonate ester [3], or by the condensation of 2-aminobenzoyl hydrazide with triethyl orthoformate [4]. Both of these claims have been subsequently shown to be incorrect [5,6]. A proported synthesis of 2-substituted-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones obtained by polyphosphoric acid cyclization of β-acyl-2-aminobenzoyl hydrazides has also been questioned [7]. Takahashi, *et al.* [8], have shown that 1-(2-aminobenzoyl)-2-(2-pyridinecarboxylic acid) hydrazide under these literature conditions yields only 2-(2-aminophenyl)-5-(2-pyridyl)-1,3,4-oxadiazole. However, the desired 2-(2-pyridyl)-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-one was obtained by treatment of *N*-(2-aminobenzoyl)-2-pyridylamidrazone with methanolic sulfuric acid. Also of relevance to the earlier Langis [7] claim is the condensation of 2-aminobenzoyl hydrazide with trimethyl orthobenzoate, which under the conditions employed (*vide infra*) yields both the oxadiazole and benzotriazepinone products. Earlier studies have shown that the condensation of orthoesters with 2-aminobenzoyl 1-methylhydrazides can be successfully utilized as a synthesis of 4-methyl-3,4-dihydro- and 4-methyl-1,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones [9,10]. Two more recent investigations deal with the formation of dihydrazides from isatoic anhydride and aromatic acyl hydrazides, and their subsequent cyclization in *p*-toluenesulfonic acid/acetic acid media [11], and with the treatment of *o*-aminobenzoyl hydrazides with triethyl orthoformate and triethyl orthoacetate [12]. Both investigations claim the synthesis of benzotriazepinones, while the latter also describes the formation of a quinazolinone product. However, there is some doubt regarding the validity of the former claim [13].

Results and Discussion.

Based on the greater nucleophilic character of the β-nitrogen atom in 2-aminobenzoyl hydrazide, preferential attack by that group on an orthoester would be expected to yield a nonisolable intermediate **2**, which upon loss of ethanol could yield either benzotriazepinones **3** or *via* an iminol tautomer, 1,3,4-oxadiazoles **4**, (Scheme I). Initial treatment of hydrazides **1a-d** with excess triethyl orthoformate (Scheme II) yielded *N*-[4(3*H*)-quinazolinon-3-yl]-formimidate esters **6** (X = H, Cl, Br, NO_2; R = Et; R^2 = R^3 = H). Only the parent compound **6a** has previously been reported [14].

Scheme I



This synthetic route appears to be a general method by which "symmetrical" (R^2 = R^3) imidate derivatives of 3-amino-4(3*H*)-quinazolinones **6** can be prepared. Indeed,

Table I

Quinazolinones **6**

Compound No. [a]	X	R^2	R^3	Reactant ratio [b]	Reaction Time hours [c]	Yield %	Mp °C (solvent) [d]	Formula [e]	Combustion Analyses % Calcd. C	H	N	Found C	H	N
6a	H	H	H	7.55	20	57	112.0-11.25 (A)	$C_{11}H_{11}N_3O_2$	60.82	5.10	19.34	60.89	5.21	19.07
6b	H	H	Me	5.24 [f]	40	98	110.0-110.2 (A)	$C_{12}H_{13}N_3O_2$	62.33	5.67	18.17	62.14	5.68	18.24
6c	H	H	Et	3.90 [g]	48	81	93-94 (B)	$C_{13}H_{15}N_3O_2$	63.66	6.16	17.13	63.70	6.02	17.29
6d	H	Me	H	1.95 [h]	120	97	80.0-81.5 (C)	$C_{12}H_{13}N_3O_2$	62.33	5.67	18.17	62.28	5.86	18.42
6e	H	Me	Me	3.00	48	72	88.0-89.0 (A)	$C_{13}H_{15}N_3O_2$	63.66	6.16	17.13	63.90	6.26	17.20
6f	H	Me	Et	3.26 [i]	192	17	66.0-67.0 (B)	$C_{14}H_{17}N_3O_2$	64.85	6.61	16.20	65.04	6.42	16.19
6g	H	Et	H	29.7 [j]	264	76	83.5-84.0 (B)	$C_{13}H_{15}N_3O_2$	63.66	6.16	17.13	63.46	6.11	17.26
6h	H	Et	Me	2.00 [k]	168	88	62.0-62.5 (B)	$C_{14}H_{17}N_3O_2$	64.85	6.61	16.70	64.94	6.60	16.38
6i	H	Et	Et	2.07	48	58	65.0-66.5 (B)	$C_{15}H_{19}N_3O_2$	65.91	7.01	15.37	66.14	7.20	15.29
6j	Cl	H	H	6.00	20 [ℓ]	65	152.0-153.5 (A)	$C_{11}H_{10}ClN_3O_2$	52.50	4.00	16.70	52.29	4.11	16.66
6k	Cl	H	Me	5.00 [m]	72	95	147.0-147.5 (A)	$C_{12}H_{12}ClN_3O_2$	54.25	4.55	15.81	54.37	4.72	15.68
6l	Cl	H	Et	13.91 [n]	312	76	127.5-128.0 (D)	$C_{13}H_{14}ClN_3O_2$	55.82	5.04	15.02	55.94	5.08	15.01
6m	Cl	Me	Me	3.10	20 [ℓ]	66	112.0-112.2 (A)	$C_{13}H_{14}ClN_3O_2$	55.82	5.04	15.02	56.10	5.23	15.03
6n	Cl	Et	Et	2.50	32 [ℓ]	40	89.0-89.5 (A)	$C_{15}H_{18}ClN_3O_2$	58.54	5.89	13.65	58.40	5.93	13.64
6o [o]	Cl	*n*-Bu	*n*-Bu	2.50	48	49	63.0-64.0 (B)	$C_{18}H_{24}ClN_3O_2$	61.80	6.90	12.01	62.00	6.93	12.10
6p	Br	H	H	6.17	240 [ℓ]	73	148.5-149.0 (A)	$C_{11}H_{10}BrN_3O_2$	44.62	3.40	14.19	44.53	3.52	14.26
6q	Br	H	Me	10.38 [p]	168 [ℓ]	78	158.0-159.0 (A)	$C_{12}H_{12}BrN_3O_2$	46.47	3.90	13.55	46.56	3.98	13.61
6r	Br	H	Et	14.91 [q]	168	76	150.5-151.0 (A/B)	$C_{13}H_{14}BrN_3O_2$	48.17	4.35	12.99	47.96	4.26	13.09
6s	Br	Me	Me	2.70	4 [ℓ]	27	146.0-148.0 (A)	$C_{13}H_{14}BrN_3O_2$	48.16	4.35	12.96	48.09	4.54	12.96
6s	Br	Me	Me	3.27	292 [r]	67	146.0-147.0 (A)							
6t	Br	Et	Et	3.00	72	82	100.0-100.1 (B)	$C_{14}H_{16}BrN_3O_2$	51.15	5.15	11.93	15.09	4.98	12.09
6u [o]	Br	*n*-Bu	*n*-Bu	2.48	40	52	75.5-76.0 (B)	$C_{18}H_{24}BrN_3O_2$	54.83	6.13	10.66	54.93	6.05	10.74
6v	NO_2	H	H	12.00	20 [s]	40	198.5-199.0 (E)	$C_{11}H_{10}N_4O_4$	50.43	4.15	21.39	50.45	4.01	21.14

[a] R^1 = Et, except where noted. [b] Ratio of orthoester to hydrazide. [c] Length of reflux with orthoester as the solvent. [d] Melting point of analytically pure product. Recrystallization solvents: A = ethanol; B = petroleum ether; C = ether; D = ethyl acetate; E = 90% ethanol/10% dioxane. [e] Analytical data were within ±0.3% for C, H, N. [f] Ratio of triethyl orthoacetate to 3-amino-4(3*H*)-quinazolinone. [g] Ratio of triethyl orthopropionate to 3-amino-4(3*H*)-quinazolinone. [h] Ratio of triethyl orthoformate to 3-amino-2-methyl-4(3*H*)-quinazolinone. [i] Ratio of triethyl orthopropionate to 3-amino-2-methyl-4(3*H*)-quinazolinone. [j] Ratio of triethyl orthoformate to 3-amino-2-ethyl-4(3*H*)-quinazolinone. [k] Ratio of triethyl orthoacetate to 3-amino-2-ethyl-4(3*H*)-quinazolinone. [ℓ] Ethanol cosolvent. [m] Ratio of triethyl orthoacetate to 3-amino-5-chloro-4(3*H*)-quinazolinone. [n] Ratio of triethyl orthopropionate to 3-amino-5-chloro-4(3*H*)-quinazolinone. [o] R^1 = Me. [p] Ratio of triethyl orthoacetate to 3-amino-5-bromo-4(3*H*)-quinazolinone. [q] Ratio of triethyl orthopropionate to 3-amino-5-bromo-4(3*H*)-quinazolinone. [r] Reaction was stirred at room temperature. [s] Cosolvent, bis-2-methoxyethyl ether.

good yields of these compounds (Table I) were obtained by the procedure described above. Quinazolinone imidates of the "mixed" type ($R^2 \neq R^3$) were prepared by treatment of a previously synthesized 3-amino-4(3*H*)-quinazolinone (**5**), with a different orthoester (Scheme II). Good yields of 6-bromo-, 6-chloro-, 6-nitro-, and unsubstituted 3-aminoquinazolinone (**5**) were obtained upon reflux of equimolar quantities of triethyl orthoformate and the requisite hydrazide **1**. Other 3-amino-4(3*H*)-quinazolinones (**5**, R^2 = Me, Et) were prepared by a different method [15]. In some cases, upon treatment of **1** with excess triethyl orthoacetate, triethyl orthopropionate, or trimethyl orthovalerate, very small quantities of the corresponding benzotriazepinone derivatives were obtained (Table II). Quinazolinone imidates **6** characteristically all displayed carbonyl stretching vibrations at 1675 ±10 cm^{-1}, imine vibrations at 1600-1630 cm^{-1}, and C-O vibrations at 1270-1330 cm^{-1}. The pmr spectra likewise displayed resonances typical of the various proton types (Table III). The special pmr solvent-induced shifts of benzene-d_6 permitted the resolution of the aromatic proton multiplets. In the case of **6a**, Ar-H_5 appeared as a doublet of doublets (J_{ortho} = 8 Hz, J_{meta} = 2 Hz) at δ 8.24, Ar-H_8 also appeared as a doublet of doublets (J_o = 8 Hz, J_m = 2 Hz) at δ 7.63, and Ar-H_6 and Ar-H_7 appeared at δ 7.15 as a quintet of doublets. The latter two proton resonances were actually two triplet of doublets which partially overlapped giving rise to the appearance of a quintet of doublets. The C_2-proton and the imino-proton both appeared as singlets at δ 8.56 and δ 7.83, respectively. The ethoxy group exhibited a methyl triplet at δ 0.90 and a methylene quartet at δ 3.90. Compounds **6b** and **6d** established the chemical shifts of the C_2-methyl

Scheme II

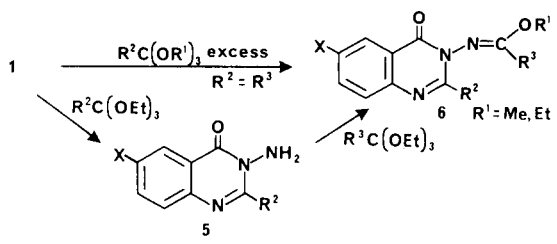


Table II

Physical and PMR Data for Benzotriazepinones **3** [a]

Compound	X	R^2	Mp °C (solvent) [b]	Yield %	Formula	N_3-H [c]	N_4-H [c]	Benzo-ring protons	R^2
3i [d]	H	Et	177.0-178.0 (ethanol)	8.7	$C_{10}H_{11}N_3O$	8.18	9.65	H_6, 7.78, dd (J = 2 Hz, 8 Hz) H_7, 7.36, td (J = 2 Hz, 8 Hz) H_8 and H_9, 6.75-7.10, m	CH_3, 1.05, t CH_2, 2.23, q
3a [e]	H	H	198.0-199.0 (ethanol)	16	$C_8H_7N_3O$	8.33	9.37	H_6, 7.82, m H_7, 7.33, td (J = 2 Hz, 8 Hz) H_8 and H_9, 6.53-7.03, m	H, 7.75, s
3n [f]	Cl	Et	177.5-178.0 (ethanol)	13	$C_{10}H_{10}ClN_3O$	8.16	9.56	H_6, 7.63, d (J = 2 Hz) H_8, 7.28, dd (J = 2 Hz, 8 Hz) H_9, 6.92, d (J = 8 Hz)	CH_3, 1.12, t CH_2, 2.27, q
3o [g]	Cl	*n*-Bu	130.0-130.5 (ethanol)	2.6	$C_{12}H_{14}ClN_3O$	6.10	8.17	H_6, 7.95, d (J = 2 Hz) H_8, 7.30, dd (J = 2 Hz, 8 Hz) H_9, 6.64, d (J = 8 Hz)	CH_3, 0.95, t *n*-PrCH_2, 2.34, t $CH_3CH_2CH_2CH_2$, 1.10-1.90, m
3s [h]	Br	Me	279.0-280.0 (ethanol)	25	$C_9H_8BrN_3O$	8.30	9.55	H_6, 7.77, d (J = 2 Hz) H_8, 7.40, dd (J = 2 Hz, 8 Hz) H_9, 6.82, d (J = 8 Hz)	CH_3, 1.96, s
3u [i]	Br	*n*-Bu	141.5-142.0 (ethanol)	10	$C_{12}H_{14}BrN_3O$	8.27	9.65	H_6, 7.92, d (J = 2 Hz) H_8, 7.41, dd (J = 2 Hz, 8 Hz) H_9, 6.95, d (J = 8 Hz)	CH_3, 0.90, t *n*-PrCH_2, 2.23, t $CH_3CH_2CH_2CH_2$, 1.10-1.90, m
3w [f]	H	Ph	256.0-256.6 (ethanol)	46	$C_{14}H_{11}N_3O$	8.51	9.76	H_6, 7.70, m H_7, 6.90, t (J = 8 Hz) H_8, 7.20-7.50, m H_9, 7.10, d (J = 7 Hz)	$H_{2'}$ and $H_{6'}$, 7.70, m; $H_{3'}$, $H_{4'}$ and $H_{5'}$, 7.20-7.50, m
3x [f]	Cl	Ph	264.0-264.5 (ethanol)	30	$C_{14}H_{10}ClN_3O$	8.75	9.93	H_6, 7.72, m H_8, 7.30-7.55, m H_9, 7.20, d (J = 8 Hz)	$H_{2'}$ and $H_{6'}$, 7.72, m; $H_{3'}$, $H_{4'}$ and $H_{5'}$, 7.30-7.55, m
3y [f]	Br	Ph	267.0-269.0 (ethanol)	22	$C_{14}H_{10}BrN_3O$	8.66	9.89	H_6, 7.80, d (J = 2 Hz) H_8, 7.40, m H_9, 7.07 d (J = 8 Hz)	$H_{2'}$ and $H_{6'}$, 7.68, m; $H_{3'}$, $H_{4'}$ and $H_{5'}$, 7.40, m
3z [f]	Me	Ph	275.0-276.0 (ethanol)	31	$C_{15}H_{13}N_3O$	8.57	9.97	H_6, H_8, and H_9, 7.10-7.90, m	X = CH_3, 2.28, s; $H_{2'}$-$H_{6'}$, 7.10-7.90, m

[a] Pmr data are listed in terms of proton type, chemical shift in δ, and multiplicity, with in some cases coupling constants. [b] Melting point of analytically pure product and recrystallization solvent. [c] Deuterium oxide exchangeable singlets. [d] Pmr solvent, DMSO-d_6; *Anal.* Calcd. for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found; C, 63.67; H, 5.85; N, 22.31. [e] Pmr solvent, DMSO-d_6. [f] Pmr solvent, 50/50 DMSO-d_6/deuteriochloroform. [g] Pmr solvent, deuteriochloroform; *Anal.* Calcd. for $C_{12}H_{14}ClN_3O$: C, 57.26; H, 5.61; N, 16.69. Found; C, 57.09; H, 5.55; N, 16.74. [h] Pmr solvent, 80/20 DMSO-d_6/deuteriochloroform. [i] Pmr solvent, DMSO-d_6; *Anal.* Calcd. for $C_{12}H_{14}BrN_3O$: C, 48.67; H, 4.76; N, 14.19. Found: C, 48.96; H, 4.80; N, 14.39.

and iminomethyl protons; the C_2-methyl protons being somewhat more deshielded. The relative chemical shifts of the three different ethyl groups (R^1, R^2, and R^3) were established by **6b**, **6h**, and **6c**, respectively; the C_2-ethyl protons were more deshielded than the iminoethyl protons and the ethoxy-group protons, the most deshielded.

One hypothesis concerning the formation of the imidate products is that the benzotriazepinones derived from kinetically-favored intermediates, **2**, thermally rearrange to 3-amino-4(3*H*)-quinazolinones (Scheme III) during the course of the reaction, which then react with excess orthoester. In an attempt to verify this hypothesis, ethanolic solutions of hydrazides **1a** and **1b** were treated with 1.10 equivalents of triethyl orthoformate. After 96 hours of stirring at ambient temperature the only products isolated were 3-amino-4(3*H*)-quinazolinones, **5a** and **5b**. Also, treatment of bromohydrazide **1c** with excess triethyl orthoacetate at ambient temperature for 792 hours gave only quinazolinone imidate **6s** in good yield. In addition to these results, the fact that 2-amino-5-nitrobenzoyl hydrazide (**1d**) upon treatment with refluxing triethyl orthoformate yielded only the quinazolinone imidate **6v**, suggests that the proposed transient intermediate **2**, may not be the major intermediate leading to the products obtained. In the case of the nitrohydrazide **1d**, one would definitely expect a benzotriazepine and/or an oxadiazole product due to the severely reduced nucleophilicity of the phenyl-ring amino group.

Plausible mechanisms for the formation of diaziridine **8** and the tautomeric benzotriazepines **3**, and their subse-

Table III

PMR Chemical Shift Data for Quinazolinones **6** [a]

Compound	Ar-H_5	Ar-H_7	Ar-H_8	R^1	R^2	R^3
6a	8.32, dd	7.35-8.00, m		CH_3, 1.38, t	H, 8.15, s	H, 8.80, s
	J = 2 Hz, 8 Hz	(X = H)		CH_2, 4.35, q		
6b	8.35, dd	7.35-7.90, m		CH_3, 1.38, t	H, 8.07, s	CH_3, 1.96, s
	J = 2 Hz, 8 Hz	(X = H)		CH_2, 4.38, q		
6c	8.37, dd	7.35-7.90, m		CH_3, 1.40, t	H, 8.12, s	CH_3, 1.15, t
	J = 2 Hz, 8 Hz	(X = H)		CH_2, 4.45, q		CH_2, 2.28, q
6d	8.20, d	7.20-7.80, m		CH_3, 1.40, t	CH_3, 2.50, s	H, 8.32, s
	J = 8 Hz	(X = H)		CH_2, 4.42, q		
6e	8.26, d,	7.35-7.80, m		CH_3, 1.45, t	CH_3, 2.48, s	CH_3, 1.90, s
	J = 8 Hz	(X = H)		CH_2, 4.48, q		
6f	8.24, d	7.20-7.80, m		CH_3, 1.42, t	CH_3, 2.50, s	CH_3, 1.10, t
	J = 8 Hz,	(X = H)		CH_2, 4.45, q		CH_2, 2.18, q
6g	8.27, dd	7.20-7.90, m		CH_3, 1.45, t	CH_3, 1.36, t	H, 8.38, s
	J = 2 Hz, 8 Hz	(X = H)		CH_2, 4.50, q	CH_2, 2.85, q	
6h	8.30, dd	7.30-7.90, m		CH_3, 1.45, t	CH_3, 1.35, t	CH_3, 1.85, s
	J = 2 Hz, 8 Hz	(X = H)		CH_2, 4.48, q	CH_2, 2.80, q	
6i	8.25, dd	7.20-7.80, m		CH_3, 1.40, t	CH_3, 1.31, t	CH_3, 1.09, t
	J = 2 Hz, 8 Hz	(X = H)		CH_2, 4.45, q	CH_2, 2.79, q	CH_2, 2.20, q
6j	8.30, d	7.65, m		CH_3, 1.42, t	H, 8,05, s	H, 8.68, s
	J = 2 Hz			CH_2, 4.36, q		
6k	8.25, d	7.63, m		CH_3, 1.40, t	H, 8.00, s	CH_3, 1.93, s
	J = 2 Hz,			CH_2, 4.42, q		
6l	8.29, d	7.70, m		CH_3, 1.45, t	H, 8.02, s	CH_3, 1.15, t
	J = 2 Hz			CH_2, 4.43, q		Ch_2, 2.24, q
6m	8.20, d	7.60, m		CH_3, 1.42, t	CH_3, 2.46, s	CH_3, 1.85, s
	J = 2 Hz			CH_2, 4.45, q		
6n	7.60, d	7.05, m		CH_3, 1.38, t	CH_3, 1.23, t	CH_3, 1.03, t
	J = 2 Hz			CH_2, 4.15, q	CH_2, 2.02, q	CH_2, 2.55, q
6o	8.20, s	7.59, m		CH_3, 3.98, s	CH_3, 0.97, t [b]	CH_3, 0.97, t [b]
					CH_3, $CH_2CH_2CH_2$, 1.20-2.10, m	
					n-PrCH_2, 2.15, t	*n*-Pr-CH_2, 2.76, t
6p	8.55, d	7.92, dd	7.73, d	CH_3, 1.52, t	H, 8.25, s	H, 8.85, s
	J = 2 Hz	J = 2 Hz, 8 Hz	J = 8 Hz	CH_2, 4.50, q		
6q	8.48, d	7.85, dd	7.64, d	CH_3, 1.40, t	H, 8.05, s	CH_3, 1.95, s
	J = 2 Hz	J = 2 Hz, 8 Hz	J = 8 Hz	CH_2, 4.42, q		
6r	8.43, d	7.79, dd	7.60, d	CH_3, 1.40, t	H, 8.00, s	CH_3, 1.10, t
	J = 2 Hz	J = 2 Hz, 8 Hz	J = 8 Hz	CH_2, 4.42, q		CH_2, 2.22, q
6s	8.40, d	7.80, dd	7.55, d	CH_3, 1.43, t	CH_3, 2.50, s	CH_3, 1.87, s
	J = 2 Hz	J = 2 Hz, 8 Hz	J = 8 Hz	CH_2, 4.48, q		
6t	8.32, d	7.75, dd	7.52, d	CH_3, 1.48, t	CH_3, 1.38, t	CH_3, 1.15, t
	J = 2 Hz,	J = 2 Hz, 8 Hz	J = 8 Hz	CH_2, 4.47, q	CH_2, 2.78, q	CH_2, 2.18, q
6u	8.35, d	7.74, dd	7.53, d	CH_3, 4.00, s	CH_3, 0.96, t [c]	CH_3, 0.94, t [c]
	J = 2 Hz	J = 2 Hz, 8 Hz	J = 8 Hz		$CH_3CH_2CH_2CH_2$, 1.10-2.00, m	
					n-PrCH_2, 2.15, t	*n*-PrCH_2, 2.76, t
6v	8.88, s	8.57, d	7.93, d	CH_3, 1.37, t	H, 8.50, s	H, 8.71, s
		J = 9 Hz	J = 9 Hz	CH_2, 4.30, q		

[a] Pmr data are listed in terms of proton type, chemical shift in δ, and multiplicity, with in some cases coupling constants. All resonances integrated for the exact number of protons of each type. Compounds **6a-6u** were run in deuteriochloroform as the solvent; **6v** was run using DMSO-d_6 as the solvent. Spectra were recorded on Varian T-60 and JEOL MH-100 proton magnetic resonance spectrometers using TMS as the internal standard. [b] Methyl triplets greately overlapped due to almost identical chemical shifts and appeared slightly distorted. [c] Methyl resonances could be differentiated due to a chemical shift difference of approximately 2 Hz.

quent conversion to quinazolinone **5** can be written. In either case, **3** → **5** or **7** → **5**, a transannular attack could occur giving rise to diaziridine intermediates **8** and **9**. The least probable mode of cyclization should be C due to the reduced nucleophilicity of the amidic amino group. Resonance stabilization of the N_1-electron pair would make route B the most probable, however, once formed either tautomer of **3** could lead to **9** because of the greater nu-

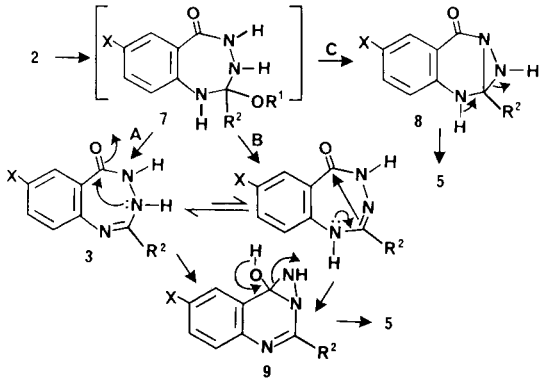
Table IV

Physical and PMR [a] Data for Oxadiazoles **4** [b]

Compound	X	R^2	Mp °C (solvent) [c]	Yield %	Formula	Substituted-Phenyl Ring Protons	R^2
4w	H	Ph	164.5-164.7 (diethyl ether)	38.8	$C_{14}H_{11}N_3O$	H_3 and H_5, 6.60-6.90, m, H_4, 7.20, t (J = 8 Hz), H_6, 7.77, d (J = 8 Hz), NH_2, 6.20, s	$H_{2'}$ and $H_{6'}$, 8.03, m, $H_{3'}$, $H_{4'}$ and $H_{5'}$, 7.46, m
4x	Cl	Ph	178.0-178.5 (diethyl ether)	52.1	$C_{14}H_{10}ClN_3O$	H_3, 6.77, d (J = 8 Hz) H_4, 7.28, dd (J = 2 Hz, 8 Hz) H_6, 7.84, d (J = 2 Hz) NH_2, 5.97, s	$H_{2'}$ and $H_{6'}$, 8.17, m $H_{3'}$, $H_{4'}$ and $H_{5'}$, 7.58, m
4y	Br	Ph	177.0-177.5 (diethyl ether)	36.9	$C_{14}H_{10}BrN_3O$	H_3, 6.73, d (J = 8 Hz) H_4, 7.33, dd (J = 2 Hz, 8 Hz) H_6, 7.95, d (J = 2 Hz) NH_2, 6.00, s	$H_{2'}$ and $H_{6'}$, 8.15, m $H_{3'}$, $H_{4'}$ and $H_{5'}$, 7.60, m
4z	Me	Ph	148.0-148.2 (diethyl ether)	52.7	$C_{15}H_{13}N_3O$	H_3, 6.65, d (J = 8 Hz) H_4, 7.00, dd (J = 2 Hz, 8 Hz) H_6, 7.50, m, CH_3, 2.23, s NH_2, 5.73, s	$H_{2'}$ and $H_{6'}$, 8.20, m $H_{3'}$, $H_{4'}$ and $H_{5'}$, 7.50, m

[a] Pmr are listed in terms of proton type, chemical shift in δ, and multiplicity, with coupling constants in some cases. All resonances integrated for the exact number of protons of each type. All samples were run in deuteriochloroform against TMS. Compounds **4w-4y** were recorded on a JEOL MH-100 spectrometer and compound **4z** was recorded on a Varian T-60. [b] The C_5-Phenyl ring is numbered $H_{2'}$ to $H_{6'}$. [c] Melting point of analytically pure product with recrystallization solvent.

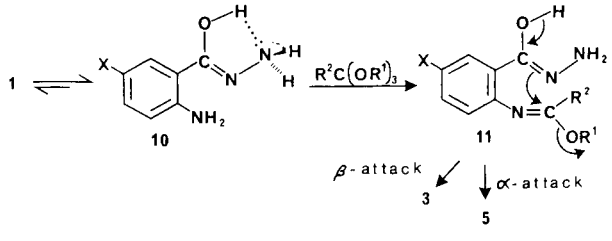
Scheme III



cleophilicity of N_3.

Considering the formation of 1,3,4-oxadiazoles, the major products of **1a-c** and **1e** (X = Me) with trimethyl orthobenzoate *versus* the formation of 5*H*-1,3,4-benzotriazepin-5-ones, the oxadiazoles should be preferred for two reasons: (1) the ease of formation of five-membered rings compared to that for seven-membered rings, and (2) the creation of an additional aromatic nucleus upon oxadiazole formation. Due to the steric bulk of the aromatic nucleus of the orthoester, attack by the β-hydrazide nitrogen occurs rather than attack by the *ortho*-amino group. Trimethyl orthobenzoate apparently reacts with the hydrazides specifically by the mechanism in Scheme I, whereas other orthoesters appear to react preferentially *via* a mechanism as proposed in Scheme IV. It is plausible that there is an equilibrium between **1** and its stabilized-hydrogen-bonded iminol tautomer **10**, which favors **10** and allows for a more favorable attack by the ortho-amino group on the sterically less hindered aliphatic orthoesters. The fact that no quinazolinone derivatives resulted in the orthobenzoate reactions suggests that a thermal rearrangement of benzotriazepinone to quinazolinone is not very likely.

Scheme IV



The oxadiazole and benzotriazepinone products were easily separated and characterized. The yellow benzotriazepinones, **3a,i,n,o,t,u,w,x,y,z** exhibited amidic carbonyl absorbances (ir) and two distinct proton singlets (pmr) for the N_3-H and N_4-H. The colorless, fluorescent oxadiazoles, **4w,x,y,z** exhibited no carbonyl absorbances (ir) and a broad singlet integrating for two protons for the amino group. Table II lists the pmr data of each benzotriazepinone obtained and Table IV lists the pmr data of each 1,3,4-oxadiazole obtained from the orthobenzoate cyclization of hydrazides **1a-c,e**.

The formation of the oxadiazoles **4** and benzotriazepinones **3** from orthobenzoate cyclization of hydrazides is particularly significant in light of the proported synthesis of benzotriazepinones reported by Langis [7]. Polyphosphoric acid cyclization of the dihydrazide formed upon treatment of isatoic anhydride with benzoyl hydrazide yielded a colorless, fluorescent compound whose melting point and spectral characteristics were identical with the 2-(2-aminophenyl)-5-phenyl-1,3,4-oxadiazole (**4w**) obtained from treatment of 2-aminobenzoyl hydrazide with trimethyl orthobenzoate. The isolation of only the oxadiazole implies that the Langis' claimed synthesis of benzotriazepinones may be in error.

The steric implications of the orthoester substituent appear to influence the mode of cyclization and the type of products obtained from these cyclization reactions. The larger the orthoester substituent, the more likely the cyclization will proceed as in Scheme I. This happens to be the case with orthobenzoate cyclization, resulting in oxadiazole **4** and benzotriazepinone **3** products. Aliphatic orthoesters however appear to proceed *via* nonisolable intermediate **11** (Scheme IV) which cyclizes by attack of the α-hydrazide nitrogen giving quinazolines (**5** → **6**) and to a lesser extent, attack of the β-hydrazide nitrogen giving benzotriazepinones **3**.

EXPERIMENTAL

Infrared spectra were obtained in potassium bromide and carbon tetrachloride in 0.10 mm cells on Sargent-Welch Pye-Unicam 3-200, and Perkin-Elmer 281B and 297 spectrophotometers. The pmr spectra were obtained in deuteriochloroform, DMSO-d_6, benzene-d_6, and mixtures of these solvents using Varian T-60 and JEOL MH-100 spectrometers. Combustion analyses were provided by M-H-W Laboratories, Phoenix, Arizona. Melting points were obtained on a Meltemp capillary melting point apparatus and are uncorrected.

Preparation of the 2-Aminobenzoyl Hydrazides **1**.

A well stirred viscous slurry of the appropriate isatoic anhydride in 95% ethanol was treated with excess 99% hydrazine. Upon cessation of carbon dioxide evolution, the product was cooled in an ice bath, then collected on a filter. Recrystallization from 95% ethanol yielded analytically pure **1**. In this manner were prepared: 2-aminobenzoyl hydrazide (**1a**) in 64% yield, mp 122-123° (lit [16] mp 123°); 2-amino-5-chlorobenzoyl hydrazide (**1b**) in 74% yield, mp 139-140° (lit [17] mp 138-139°); 2-amino-5-bromobenzoyl hydrazide (**1c**) [18] in 65% yield, mp 142-143°; 2-amino-5-nitrobenzoyl hydrazide (**1d**) in 76% yield, mp 225-226° (lit [19] mp 214-218°) and 2-amino-5-methylbenzoyl hydrazide (**1e**) in 89% yield, mp 138.0-138.5° (lit [20] mp 137-139°).

5-Bromoisatoic Anhydride.

Chromium trioxide oxidation [21] in acetic acid yielded product in 82% yield. Recrystallization from dioxane gave analytically pure orange needles, mp 295° dec (lit [21] mp 286-288°).

5-Methylisatoic Anhydride.

A modified procedure similar to that of Grosso [22] was utilized for the synthesis fo 5-methylisatoic anhydride. Treatment of 5-methylanthranilic acid (0.20 mole) with ethyl chloroformate (1.00 mole) followed by 48 hours of refluxing gave upon filtration 8.16 g (50%) of anhydride, mp 249-250° dec (lit [20] 248-250°). Evaporation of the excess chloroformate gave ethyl *N*-carboethoxy-5-methylanthranilate. Recrystallization from petroleum ether gave 14.24 g (23%) of analytically pure needles, mp 46.0-46.5°; ir (potassium bromide): 3260 (NH), 1730 (ester C=O), 1685 (urethane C=O), 1215, 1240, and 1260 (C-O); nmr (deuteriochloroform): 1.33 (overlapping t, 6, OCH_2CH_3), 2.27 (s, 3, C_5-CH_3), 4.23 (overlapping q, 4, OCH_2CH_3), 7.27 (d, J = 8 Hz, 1, C_3-H), 7.73 (s, 1, C_6-H), 8.30 (d, J = 8 Hz, 1, C_4-H), 10.36 (s, 1, N-H).

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.85; N, 5.57. Found: C, 62.10; H, 7.00; N, 5.65.

A General Procedure for the Preparation of 3-Amino-4(3*H*)-quinazolinones **5**.

Fifty mmoles of the requisite hydrazide **1** dissolved in 50 ml of 95% ethanol were added to a slight excess of triethyl orthoformate; in the case of **5d**, a 275 mole percent excess of orthoformate was utilized. The reaction was heated at reflux temperature for 24 hours. After cooling in an ice bath, the product was collected on a filter. Evaporation of the filtrate *in vacuo* yielded an additional crop of product. The combined solids were washed with a diethyl ether/ethanol (90/10) mixture, and then were recrystallized from the appropriate solvent.

3-Amino-4(3*H*)-quinazolinone (**5a**).

This compound was obtained in a yield of 60%, mp 209-211° (ethanol), (lit mp 204°) [23]; ir (potassium bromide): 3300 and 3170 (N-H), 1680 (C=O); 1630 (C=N); nmr (DMSO-d_6): δ 5.78 (s, 2, NH_2), 7.66-8.10 (m, 4, Ar-H), 8.32 (s, 1, C_2-H).

3-Amino-6-chloro-4(3*H*)-quinazolinone (**5b**).

This compound was obtained in a yield of 63%, mp 225.0-225.2° (glacial acetic acid), (lit mp 225-226°) [17]; ir (potassium bromide): 3310 and 3190 (N-H), 1680 (C=O); 1630 (C=N); nmr (DMSO-d_6): δ 5.83 (s, 2, NH_2), 7.70 (m, 2, C_7-H and C_8-H), 8.11 (s, 1, C_2-H), 8.34 (d, J = 2 Hz, 1, C_5-H).

3-Amino-6-bromo-4(3*H*)-quinazolinone (**5c**).

This compound was obtained in a yield of 81%, mp 224-225° (1,2-dimethoxyethane), (lit mp 227-228°) [24]; ir (potassium bromide): 3420 and 3315 (N-H), 1665 (C=O); 1630 (C=N, shoulder); nmr (DMSO-d_6): δ 5.80 (s, 2, NH_2), 7.77 (d, J = 8 Hz, 1, C_8-H), 7.97 (dd, J = 2 Hz and 8 Hz C_7-H), 8.29 (s, 1, C_2-H), 8.60 (d, J = 2 Hz, 1, C_5-H).

3-Amino-6-nitro-4(3*H*)-quinazolinone (**5d**).

This compound was obtained in a yield of 77%, mp 210.0-210.5° (glacial acetic acid), (lit mp 170-171°) [19]; ir (potassium bromide): 3320 and 3210 (N-H), 1680 (C=O); 1610 (C=N), 1510 and 1340 (NO_2); nmr (DMSO-d_6): δ 5.92 (s, 2, NH_2), 7.85 (d, J = 8 Hz, 1, C_8-H), 8.48 (d, J = 8 Hz, 1, C_7-H), 8.52 (s, 1, C_2-H), 8.82 (s, 1, C_5-H).

Treatment of 2-Aminobenzoyl Hydrazide (**1a**) with Triethyl Orthoformate.

To a solution of 3.02 g (20 mmoles) of **1a** in 100 ml of absolute ethanol was added 3.30 g (22 mmoles) of triethyl orthoformate. The solution was stirred at ambient temperature for 96 hours. The solid which had precipitated was collected on a filter. The filtrate was then concentrated *in vacuo* giving additional solid. The solids were recrystallized from ethanol giving recovered **1a** and 1.35 g (55% based on recovered **1a**) of pure **5a**, mp 206.5-207.5°; ir (potassium bromide): was identical to that of **5a** obtained from the refluxed reaction.

Treatment of 2-Amino-5-chlorobenzoyl Hydrazide (**1b**) with Triethyl Orthoformate.

A solution of 2-amino-5-chlorobenzoyl hydrazide (3.70 g, 20 mmoles) in 100 ml of absolute ethanol was prepared and was mixed with 3.30 g (22 mmoles) of triethyl orthoformate. This solution was then stirred at ambient temperature for 96 hours. After filtration, the filtrate was concentrated and the solid which was obtained, with the initial crop, was recrystallized from diglyme. Pure **5b**, mp 217-219° was obtained in 44% yield (based on recovered **1b**); ir (potassium bromide): was identical to that of **5b** obtained from the refluxed reaction.

Treatment of 2-Amino-5-bromobenzoyl Hydrazide (**1d**) with Triethyl Orthoacetate.

A mixture of 3.45 (15 mmoles) of **1d** and 8.00 g (49 mmoles) of triethyl orthoacetate was stirred at ambient temperature for 792 hours. The reaction was then concentrated *in vacuo* and gave 3.34 g (69%) of quinazolinone imidate **6s**. Recrystallization from diethyl ether gave analytically pure needles of **6s**, mp 146-147°; nmr (deuteriochloroform) was identical to that of **6s** obtained from the refluxed reaction.

A General Procedure for the Preparation of Quinazolinone Imidates **6** from Hydrazides **1**.

A mixture of the requisite hydrazide **1a-d** in excess (two equivalents or more) orthoformate, orthoacetate, orthopropionate, or orthovalerate (with and without a cosolvent) was heated at reflux for at least 20 hours. After cooling the reaction was concentrated *in vacuo* and the product collected on a filter and dried *in vacuo*. Recrystallization from the appropriate solvent gave analytically pure crystalline product. Yields and properties of **6** are reported in Tables I and III.

Ethyl *N*-[4(3*H*)-Quinazolinon-3-yl]formimidate (**6a**) and 3,4-Dihydro-5*H*-1,3,4-benzotriazepin-5-one (**3a**).

Hydrazide **1a** (3.02 g, 20 mmoles) and 20 ml of triethyl orthoformate were heated at reflux for 24 hours. While hot the reaction was filtered and the filtrate concentrated *in vacuo*. The quinazolinone **6a** obtained was separated from the benzotriazepinone **3a** by recrystallization from diethyl ether. The quinazolinone imidate (2.48 g, 57%) was recrystallized from ethanol giving analytically pure needles of **6a**, mp 112.0-112.5°; ir (potassium bromide): 1675 (C=O), 1600 (C=N), 1290 (C-O).

Anal. Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.89; H, 5.21; N, 19.07.

A small amount of 3-amino-4(3*H*)-quinazolinone (**5a**) (0.40 g, 12%) was separated from the benzotriazepinone **3a** by fractional recrystallization from ethanol, mp 209-210°.

Recrystallization of **3a** from ethanol gave analytically pure yellow crystals (0.50 g, 16%), mp 198-199°; ir (potassium bromide): 3280 and 3200 (N-H, broad), 1695 (C=O), 1625 (C=N).

Anal. Calcd. for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.60; H, 4.49; N, 26.26.

Ethyl *N*-[6-Chloro-2-ethyl-4(3*H*)-quinazolinon-3-yl]propionimidate (**6n**) and 7-Chloro-2-ethyl-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-one (**3n**).

To 44.50 g (0.25 mole) of refluxing triethyl orthopropionate was added a hot solution of 18.56 g (0.10 mole) of hydrazide **1b** in 150 ml of absolute ethanol. After 24 hours of refluxing, the ethanol was removed by distillation. Reflux was terminated after 40 hours and the reaction was cooled in an ice bath. The crystallized product was collected on a filter, dried *in vacuo*, then recrystallized from diethyl ether. Analytically pure **6n** (12.31 g, 40%) was obtained as colorless needles from petroleum ether, mp 89.0-89.5°; ir (carbon tetrachloride): 1680 (C=O), 1610 (C=N), 1595 (Ar, C=C), 1320 (C-O).

Anal. Calcd. for $C_{15}H_{18}ClN_3O_2$: C, 58.54; H, 5.89; N, 13.65. Found: C, 58.40; H, 5.93; N, 13.64.

The 7-chloro-2-ethylbenzotriazepinone (**3n**) which remained was recrystallized from ethanol as fine yellow needles (2.99 g, 13%), mp 177.5-180.0°; ir (potassium bromide): 3260 and 3200 (N-H, broad), 1680 (C=O), 1620 (C=N).

Anal. Calcd. for $C_{10}H_{10}ClN_3O$: C, 53.70; H, 4.51; N, 18.79. Found: C, 53.49; H, 4.48; N, 18.95.

Ethyl *N*-[6-Bromo-2-methyl-4(3*H*)-quinazolinon-3-yl]acetimidate (**6s**) and 7-Bromo-2-methyl-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-one (**3s**).

A solution containing 9.20 g (40 mmoles) of hydrazide **1c** in 150 ml of absolute ethanol was added over a period of 2 hours to 17.60 g (110 mmoles) of refluxing triethyl orthoacetate. The reaction was heated at reflux for 4 hours then was concentrated *in vacuo*. The product which crystallized was dissolved in diethyl ether leaving behind the benzotriazepinone **3s**. Evaporation of the ether gave quinazolinone **6s** (3.46 g, 27%). Recrystallization from ethanol gave analytically pure **6s** as colorless needles, mp 146.0-148.0°; ir (carbon tetrachloride): 1685 (C=O), 1625 (C=N), 1595 (Ar, C=C), 1320 (C-O).

Anal. Calcd. for $C_{13}H_{14}BrN_3O$: C, 48.16; H, 4.35; N, 12.96. Found: C, 48.09; H, 4.54; N, 12.96.

Benzotriazepinone **3s** was recrystallized from ethanol and gave 2.49 g (25%) of analytically pure yellow needles, mp 279.0-280.0°; ir (potassium bromide): 3260 and 3200 (N-H, broad), 1680 (C=O), 1600 (C=N).

Anal. Calcd. for $C_9H_8BrN_3O$: C, 42.54; H, 3.17; N, 16.54. Found: C, 42.61; H, 3.00; N, 16.38.

A General Procedure for the Preparation of Quinazolinone Imidates **6** from 3-Amino-4(3*H*)-quinazolinones **5**.

The requisite 3-aminoquinazolinone **5** was heated at reflux in excess orthoester for a minimum of 40 hours. Upon completion of reflux the solution was concentrated *in vacuo*. The solid thus obtained was collected on a filtered and dried *in vacuo*. Recrystallization from the appropriate solvent gave analytically pure quinazolinone imidate **6**.

Ethyl *N*-[4(3*H*)-quinazolinon-3-yl]acetimidate (**6b**).

Four g (21 mmoles) of 3-amino-4(3*H*)-quinazolinone (**5a**) was added to 20 ml of triethyl orthoacetate and was heated at reflux for 40 hours. Upon cooling in an ice bath the product precipitated. Initial recrystallization of the product from petroleum ether gave 4.76 g (98%) pure quinazolinone imidate. Analytically pure **6b** was obtained by recrystallization from ethanol, mp 110.0-110.2°; ir (carbon tetrachloride): 1680 (C=O), 1622 (C=N), 1600 (Ar, C=C), 1310 (C-O).

Anal. Calcd. for $C_{12}H_{12}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.14; H, 5.68; N, 18.24.

Ethyl *N*-[2-Methyl-4(3*H*)-quinazolinon-3-yl]formimidate (**6d**).

Six g (34 mmoles) of 3-amino-2-methyl-4(3*H*)-quinazolinone were heated at reflux in 10.00 g (67 mmoles) of triethyl orthoformate and were converted to 7.60 g (97%) of **6d** by the general procedure, colorless needles, mp 80.0-81.5°; ir (carbon tetrachloride): 1685 (C=O), 1620 (C=N), 1600 (Ar, C=C), 1265 (C-O).

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.28; H, 5.86; N, 18.42.

Ethyl *N*-[5-Chloro-4(3*H*)-quinazolinon-3-yl]acetimidate (**6k**).

Quinazolinone **5b** (5.35 g, 24 mmoles) was heated at reflux in 19.08 g (120 mmoles) of triethyl orthoacetate and was converted to **6k** (6.06 g, 95%) according to the general procedure; colorless needles, mp 147.0-147.5°; ir (carbon tetrachloride): 1690 (C=O), 1620 (C=N), 1600 (Ar, C=C), 1315 (C-O).

Anal. Calcd. for $C_{12}H_{12}ClN_3O_2$: C, 54.25; H, 4.55; N, 15.81. Found: C, 54.37; H, 4.72; N, 15.68.

Ethyl *N*-[5-Chloro-4(3*H*)-quinazolinon-3-yl]propionimidate (**6ℓ**).

Quinazolinone imidate **6ℓ** was prepared in 76% yield by treatment of quinazolinone **5b** (3.40 g, 15 mmoles) with triethyl orthopropionate (36.79 g, 210 mmoles) according to the general procedure, colorless needles, mp 127.5-128.0°; ir (carbon tetrachloride): 1685 (C=O), 1610 (C=N, shoulder), 1600 (Ar, C=C), 1320 (C-O).

Anal. Calcd. for $C_{13}H_{14}ClN_3O_2$: C, 55.82; H, 5.04; N, 15.02. Found: C, 55.94; H, 5.08; N, 15.01.

2-Phenyl-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-one (**3w**) and 2-(2-Aminophenyl)-5-phenyl-1,3,4-oxadiazole (**4w**).

A solution of hydrazide **1a** (7.55 g, 50 mmoles) dissolved in 75 ml of methanol was treated with 13.67 g (75 mmoles) of trimethyl orthobenzoate and was then heated at reflux for 48 hours. The precipitate which had formed was collected on a filter. The oxadiazole **4w** was separated from the benzotriazepinone by boiling in diethyl ether. Recrystalization of oxadiazole **4w** from ether gave 3.06 g (39%) of analytically pure product, mp 164.5-164.7°; ir (potassium bromide): 3420 and 3220 (N-H), 1620 (C=N), 1610 (Ar, C=C).

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

C, 70.93; H, 4.62; N, 18.00.

The yellow benzotriazepinone which remained was recrystallized from ethanol and gave 5.30 g (46%) of analytically pure **3w** as yellow needles, mp 256.0-256.5°; ir (potassium bromide): 3300 and 3180 (N-H), 1655 (C=O), 1605 (C=N).

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.72; H, 4.47; N, 17.94.

7-Chloro-2-phenyl-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-one (**3x**) and 2-(2-Amino-5-chlorophenyl)-5-phenyl-1,3,4-oxadiazole (**4x**).

To 7.42 g (40 mmoles) of hydrazide **1b** which was dissolved in 40 ml of ethanol were added 9.10 g (50 mmoles) of trimethyl orthobenzoate. The mixture was heated at reflux for 24 hours then cooled in an ice bath. The precipitate was collected on a filter and the filtrate was concentrated *in vacuo* giving 1.40 g of recovered **1b**. The oxadiazole was separated from the benzotriazepinone by boiling in ether. Analytically pure oxadiazole **4x** (4.60 g, 52% based on recovered **1b**) was obtained as colorless needles from ether, mp 178.0-178.5°; ir (potassium bromide): 3420 and 3320 (N-H), 1620 (C=N).

Anal. Calcd. for $C_{14}H_{10}ClN_3O$: C, 61.89; H, 3.71; N, 15.47. Found: C, 61.67; H, 3.68; N, 15.57.

The benzotriazepinone which remained was recrystallized from ethanol and gave 2.62 g (30% based on recovered **1b**) of **3x** as analytically pure yellow needles, mp 264.0-264.5°; ir (potassium bromide): 3260 and 3200 (N-H), 1655 (C=O), 1610 (C=N).

Anal. Calcd. for $C_{14}H_{10}ClN_3O$: C, 61.89; H, 3.71; N, 15.47. Found: C, 61.94; H, 3.59; N, 15.36.

7-Bromo-2-phenyl-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-one (**3y**) and 2-(2-Amino-5-bromophenyl)-5-phenyl-1,3,4-oxadiazole (**4y**).

Treatment of 4.60 g (20 mmoles) of hydrazide **1c** with 5.00 g (27 mmoles) of trimethyl orthobenzoate according to the procedure described for **3w** and **4w**, yielded 2.21 g (37%, based on recovered **1c**) of oxadiazole **4y**, mp 177.0-177.5°; ir (potassium bromide): 3460 and 3310 (N-H), 1610 (C=N).

Anal. Calcd. for $C_{14}H_{10}BrN_3O$: C, 53.19; H, 3.19; N, 13.29. Found: C, 53.06; H, 3.24; N, 13.19.

Benzotriazepinone **3y** (1.30 g) was also obtained in 22% yield (based on recovered **1c**) from ethanol as yellow needles, mp 267.0-269.0°; ir (potassium bromide): 3240 and 3200 (shoulder) (N-H), 1640 (C=O), 1600 (C=N).

Anal. Calcd. for $C_{14}H_{10}BrN_3O$: C, 53.19; H, 3.19; N, 13.29. Found: C, 53.24; H, 3.28; N, 13.29.

7-Methyl-2-phenyl-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-one (**3z**) and 2-(2-Amino-5-methylphenyl)-5-phenyl-1,3,4-oxadiazole (**4z**).

Hydrazide **1e** (3.31 g, 20 mmoles) was treated with trimethyl orthobenzoate (4.50 g, 25 mmoles) according to the procedure described for **3w** and **4w**. Oxadiazole **4z** was obtained in 53% yield, mp 148.0-148.2°; ir (potassium bromide): 3410 and 3320 (N-H), 1630 (C=N).

Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.68; H, 5.23; N, 16.87.

Benzotriazepinone **3z** was also obtained in 31% yield as pure yellow needles, mp 275.0-276.0°; ir (potassium bromide): 3260 (broad N-H), 1660 (C=O), 1620 (C=N), 1600 (Ar, C=C).

Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.58; H, 5.12; N, 16.87.

Acknowledgements.

The author wishes to thank the Sherwin Williams Company for their generosity in supplying samples of isatoic anhydride, chloroisatoic anhydride, and nitroisatoic anhydride.

REFERENCES AND NOTES

[1] Presented at the 17th Middle Atlantic Regional ACS Meeting, Organic Chemistry Section, White Haven, PA, April 6, 1983.

[2a] S. Toyoshima, Japanese Patent 7,011,148; *Chem. Abstr.*, **73**, 25544a (1970); [b] S. Toyoshima, Japanese Patent 7,011,148; *Chem. Abstr.*, **73**, 25545b (1970); [c] T. Sulkowski and S. Childress, *J. Med. Chem.*, **7**, 386 (1964); [d] T. Sulkowski and S. Childress, U. S. Patent 3,176,008; *Chem. Abstr.*, **62**, 162841 (1965).

[3] C. Podesva, G. Kohan and K. Vagi, *Can. J. Chem.*, **47**, 489 (1969).

[4] G. T. Panse and S. K. Kamat, *Indian J. Chem.*, **46**, 834 (1973).

[5] M. J. Kornet, *J. Pharm. Sci.*, **62**, 834 (1973).

[6] N. P. Peet, S. Sunder and D. L. Trepanier, *Indian J. Chem.*, **14**, 701 (1976).

[7] A. Langis, U. S. Patent 3,542,767; *Chem. Abstr.*, **74**, 88089x (1971).

[8] M. Takahashi, S. Onizawa and T. Satoh, *Bull. Chem. Soc. Japan*, **47**, 2724 (1974).

[9] S. Sunder, N. P. Peet and D. L. Trepanier, *J. Org. Chem.*, **41**, 2732 (1976).

[10] R. W. Leiby and N. D. Heindel, *J. Org. Chem.*, **41**, 2736 (1976).

[11] C. K. Reddy, P. S. N. Reddy and C. V. Ratnam, *Synthesis*, 842 (1983).

[12] J. Y. Merour, *J. Heterocyclic Chem.*, **19**, 1425 (1982).

[13] N. P. Peet, *Synthesis*, in press.

[14] M. Vincent, J. Millard and M. Bernard, *Bull. Soc. Chim. France*, 1580 (1962).

[15] R. W. Leiby, submitted to *J. Org. Chem.*, October 3, 1984.

[16] C. Thode, *J. Prakt. Chem.*, **69**, 92 (1904).

[17] C. Casagrande, M. Canova and G. Ferrari, *Farmaco (Pavia), Ed. Sci.*, **20**, 544 (1965).

[18] F. Russo, A. Santagati and M. Santagati, *Farmaco Ed. Sci.*, **37**, 719 (1982).

[19] Kratz, *J. Prakt. Chem.*, **53**, 222 (1896).

[20] J. C. Sircar, T. Capiris, S. J. Kesten and D. J. Herzig, *J. Med. Chem.*, **24**, 735 (1981).

[21] R. Adams and H. Synder, *J. Am. Chem. Soc.*, **60**, 1412 (1938).

[22] J. A. Grosso, D. E. Nichols, J. D. Kohli and D. Glock, *J. Med. Chem.*, **25**, 703 (1982).

[23] V. S. Dighe, S. Somasekhara, G. Bagavant and S. L. Mukherjee, *Current Sci. (India)*, **33**, 78 (1964).

[24] S. E. Cairncross and M. T. Bogert, *Collect. Czech. Chem. Commun.*, **7**, 548 (1935).