Synthesis of 3-Amino-4(3*H*)-quinazolinones from *N*-(2-Carbomethoxyphenyl) Imidate Esters[1]

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Novel difunctional aromatic synthons consisting of *N*-(2-carbomethoxyphenyl) imidate esters were synthesized by treatment of methyl anthranilate esters with aliphatic ortho esters. Treatment of the imidates with hydrazine, methylhydrazine, and phenylhydrazine yielded only quinazolinones and not isomeric 1,3,4-benzotriazepin-5-ones. The type of products obtained gave information relevant to elucidation of the mechanism of cyclization and the relative reactivities of the ester and imidate groups.

The recent interest in benzotriazepines as pharmacological agents possessing central nervous system activity has stimulated a great deal of research toward the synthesis of these agents. Hydrazides[2] of anthranilic acid bearing α-methyl substituents have been found to yield 1,3,4-benzotriazepines via condensation with ortho esters.[3] Other potentially useful ortho-difunctional compounds capable of yielding benzotriazepines upon treatment with hydrazines have been prepared. One such preparation consists of the treatment of 2-aminobenzophenones and methyl anthranilate with diethyl (ethoxymethylene)-malonate.[4] However, in the case of the anthranilate ester adducts, treatment with hydrazine was found to yield 3-amino-4(3*H*)-quinazolinones and not the anticipated 1,3,4-benzotriazepin-5-ones.[5] Another approach entails the synthesis of imidate esters of substituted 2-amino-benzophenones via treatment of the benzophenone with triethyl orthoacetate and substituted triethyl ortho-glycinates.[6] These imidate esters also yielded quinazoline products upon treatment with hydrazine and glycinyl hydrazides. Simple monofunctional imidate esters have been employed in the synthesis of derivatives of 4-pyrimidone.[7] Other anthranilic acid derivatives, such as *N*-acylanthranilic acids[8] and 3,1-benzoxazin-4-ones[9,10] have been utilized as precursors of 4(3*H*)-quinazolinones. This research is concerned with the synthesis of *N*-(2-carbomethoxyphenyl) imidate esters and their reactions with various hydrazines.

The synthesis of methyl 2-[(ethoxymethylene)amino]-benzoate and its condensation with 1-acetyl-1-methylhydrazine has been previously described.[11] In order to investigate the possible steric effects of the ortho ester substituents and the electronic effects of the substituents on the anthranilate substrate and to verify the utility of the synthetic method, a number of other *N*-(2-carbomethoxyphenyl) imidate esters have been synthesized.

Stoichiometry appears to be a critical consideration in the synthesis of *N*-(2-carbomethoxyphenyl) imidate esters. These esters were prepared by premixing the ortho ester and anthranilate, followed by reflux, and by periodic addition of the anthranilate ester to refluxing ortho ester (Scheme I). In either case, however, to ensure optimum yields of products, an excess of ortho ester had to be employed. This was particularly important in the cases of formimidates **3a** and **3d**, which were derived from triethyl orthoformate (Table I). Employment of an extremely large excess of orthoformate compared to methyl 5-chloroanthranilate in the formation of imidate **3d** resulted in a small but significant yield of quinazolinone **4d**. This result implies that condensation of the reactants appears to be a moderately slow process, since upon formation of the formimidate **3d**, condensation of it with a second molecule of anthranilate ester does occur even in a fairly dilute solution. Larger yields of quinazolinone **4** can be achieved with smaller orthoformate/anthranilate ratios, as in the case of **3a**. Imidate esters derived from triethyl orthoacetate and triethyl orthopropionate were obtained in excellent yields even with reactant ratios as low as 1.3.

Scheme I

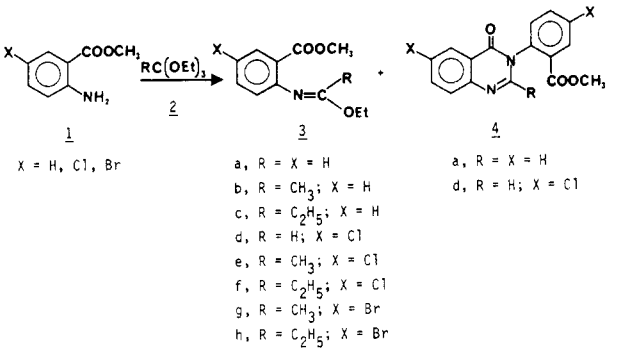

Table I. Physical Data for *N*-(2-Carbomethoxyphenyl) Imidate Esters 3

compd	X	R	reactant ratio (2/1)	reflux duration, h	% yield	bp,[a] °C (mm)
3a[b]	H	H	1.5 (**2a**/**1a**)		45.0	91 (0.10)
3a	H	H	2.0 (**2a**/**1a**)	48	38.4	135–138 (6.00)
3b	H	Me	1.3 (**2b**/**1a**)	32	70.1	80–84 (0.25)
3c	H	Et	1.3 (**2c**/**1a**)	48	88.8	124–125 (1.00)
3d	Cl	H	24.0 (**2a**/**1b**)	72	66.7	110–111 (0.45)
3e	Cl	Me	2.8 (**2b**/**1b**)	72	90.2	108.0–108.5 (0.25)
3f	Cl	Et	4.4 (**2c**/**1b**)	65	83.6	134–136 (1.30)
3g	Br	Me	4.6 (**2b**/**1c**)	72	93.6	128–129 (0.45)
3h	Br	Et	3.7 (**2c**/**1c**)	72	85.6	118–119 (0.30)

[a] Bp of analytically pure **3**. [b] Reference 3. A quantity of quinazolinone **4** was obtained but not isolated.

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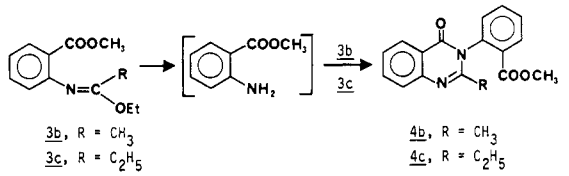
Table II. Physical Data for Unsubstituted and Substituted 3-Amino-4(3*H*)-quinazolinones 7

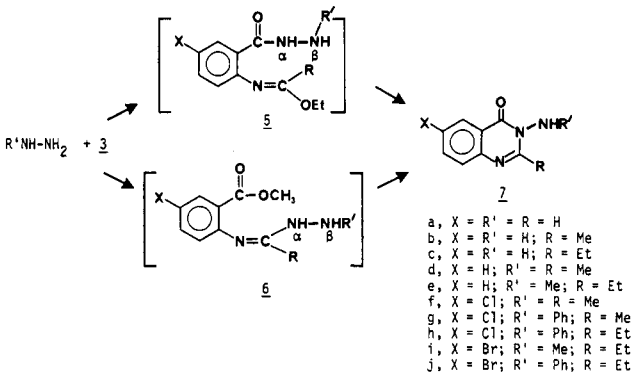
compd	X	R	R′	reactant ratio (3/R′NHNH$_2$)	reflux duration, h	% yield	mp,[a] °C
7a[b]	H	H	H	1.0 (**3a**/N_2H_4)	0[c]	56.2	210–211
7b[d]	H	Me	H	1.1 (**3b**/N_2H_4)	0.25	79.1	146–148
7c[e]	H	Et	H	1.3 (**3c**/N_2H_4)	1.0	74.5	117–118
7d[f]	H	Me	Me	1.6 (**3b**/MeNHNH$_2$)	4.0	62.2	108–109
7e	H	Et	Me	1.2 (**3c**/MeNHNH$_2$)	5.0	87.0	93.0–93.5
7f[g]	Cl	Me	Me	1.1 (**3e**/MeNHNH$_2$)	20	65.9	134.0–134.2
7g	Cl	Me	Ph	1.1 (**3e**/PhNHNH$_2$)	20	63.9	195–196
7h	Cl	Et	Ph	1.1 (**3f**/PhNHNH$_2$)	20	62.8	131.0–131.5
7i	Br	Et	Me	1.3 (**3h**/MeNHNH$_2$)	20	73.8	159–160
7j	Br	Et	Ph	1.2 (**3h**/PhNHNH$_2$)	20	65.7	145.5–146.0

[a] Melting point of analytically pure quinazolinone. [b] Reference 18; lit. mp 204 °C. [c] Reaction was run at room temperature. [d] Reference 18; lit. mp 146–148 °C. [e] Reference 19; lit. mp 152–153 °C. [f] Reference 20; lit. mp 110–111 °C. [g] Reference 11; lit. mp 132–133 °C.

Scheme II



Scheme III



The difference in reactivity of the formimidates compared to that of the acetimidates and propionimidates presumably arises from steric hindrance created by the alkyl groups in the latter two imidates. Once formed, the acetimidates and propionimidates appear to be impervious to further attack by the anthranilate ester remaining in the reaction medium.

The imidate esters were easily characterized by their infrared and ^{1}H NMR spectra. All compounds exhibited typical proton resonances for their alkyl and alkoxy groups. The formimidate protons of the parent ester **3a** and its 5-chloro analogue **3d** both appeared as singlets in the aromatic region. The aromatic protons were all differentiable, even in the cases of unsubstituted esters **3a**, **3b**, and **3c**. The aromatic splitting patterns and coupling constants of the chloro imidates were identical with those of their precursor, methyl 5-chloroanthranilate, although the chemical shift of the imidate protons showed that they were determinately less shielded than those of the chloroanthranilate. This similarity is significant when comparison with the quinazolinone products is made (vide infra).

Infrared carbonyl and imine absorbances appeared as strong, overlapping bands occurring at 1732 and 1677 cm^{-1}, respectively. The formimidates, however, exhibited imine bands at 1650 cm^{-1}, approximately 30 cm^{-1} lower than the other imidate esters. A possible rationale for a lower absorption frequency might be that a greater degree of planarity of the imine and aromatic moieties can be achieved in the formimidates. Steric hindrance of the methyl and ethyl substituents in the acetimidates and propionimidates could restrict the two moieties from attaining planarity thereby raising the stretching frequency.

Quinazolinones **4a** and **4d**, which appeared as undesirable byproducts of the imidate synthesis, also resulted from the slow hydrolytic cleavage of the imidate functionality. The initially formed anthranilate esters give rise to these quinazolinones upon reaction with the imidates (Scheme II). These quinazolinones exhibited typical ester, amide carbonyl, and imine stretching frequencies in the infrared spectra. The ^{1}H NMR spectra also exhibited all of the expected resonances.

Treatment of the imidate esters with hydrazine, methylhydrazine, and phenylhydrazine resulted in the formation of quinazolinones[12] as the sole products (Scheme III). None of the isomeric 1,3,4-benzotriazepin-5-ones were isolated, implying that a regiospecific attack by the least hindered nitrogen of the hydrazines had occurred. Even in the reactions employing methylhydrazine, the least hindered nitrogen attacked rather than the most nucleophilic. In the cases of carboxylic anhydrides[13] and isatoic anhydrides,[2] the methyl nitrogen of the methylhydrazine is acylated, whereas the opposite is true for carboxylic esters. Apparently, the reactivity of the imidate functionality does not quite approach that of the anhydride. However, one would expect the reactivity of the imidate to exceed that of the ester due to the stabilization of the incipient anion throughout the aromatic system. This type of regiospecificity has been shown to exist in the conversion of 2-methyl-3,1-benzoxazin-4-one to quinazolinones.[10] Upon attack of aniline on acetylanthranil, ring opening occurs with cleavage of the C_2–O_3 bond, giving rise to an *o*-amidiniobenzoate salt. This salt was shown to cyclize to the quinazolinone product in the presence of pyridine or toluene. Existence of the salt was confirmed by its salt-like infrared spectrum and by decomposition in aqueous acetone to *N*-acetylaminobenzoic acid.

An additional consideration in the proposed mechanism is the difference in reactivity of a hydrazide moiety vs. that of an amidrazone moiety. If the reaction were to proceed via hydrazide intermediate **5**, the preferred mode of cyclization would yield 1,3,4-benzotriazepin-5-ones due to the greater nucleophilicity of the β-nitrogen with respect to that of the α-nitrogen. Since the benzotriazepinones do

(12) Quinazolinone **7a** was also prepared by treatment of 2-aminobenzohydrazide with a slight excess of triethyl orthoformate. Quinazolinones **7b** and **7c**, prepared by this procedure, were utilized as precursors to ethyl *N*-[2-methyl-4-oxo-3,4-dihydroquinazolin-3-yl]formimidate, ethyl *N*-[2-ethyl-4-oxo-3,4-dihydroquinazolin-3-yl]formimidate, ethyl *N*-[2-ethyl-4-oxo-3,4-dihydroquinazolin-3-yl]acetimidate, and ethyl *N*-[2-methyl-4-oxo-3,4-dihydroquinazolin-3-yl]propionimidate: Leiby, R. W. *J. Heterocycl. Chem.* **1984**, *21*, 1825.

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not result, the proposed existence of an amidrazone (6) intermediate appears plausible. The preferred tautomer would be expected to be that in which the C=N bond is in conjugation with the aromatic ring. In either tautomer, the nucleophilicity of the α-amidrazone nitrogen should exceed that of the α-nitrogen in 5, thus leading to quinazolinone 7 formation.

The ^{1}H NMR spectra of the product quinazolinones exhibited the appropriate resonances for the particular groups each contained. A major alteration in the aromatic resonances occurred upon cyclization to the quinazolinones. Imidates **3b** and **3c** exhibited distinct ortho-coupled doublets for Ar H_6 and Ar H_3, while Ar H_4 and Ar H_5 each appeared as a triplet of doublets. The quinazolinones derived from these imidates exhibited ortho-coupled doublets for the C_5 protons, which are significantly more deshielded than the corresponding imidate protons. This enhanced deshielding effect, which also occurs in the chloro analogues, can be rationalized by a greater planarity of the carbonyl in the quinazolinones relative to that of the imidates. The remaining aromatic protons appeared as undifferentiable multiplets. Chloroimidates **3d–f** likewise exhibited clearly differentiated aromatic resonances consisting of ortho-coupled doublets for C_6H, doublet of doublets for C_5H, and doublets for C_3H. The aromatic chloroquinazolinone protons simply consisted of a meta-coupled doublet for C_5H and a less deshielded, slightly distorted singlet for C_7H and C_8H. A plausible basis for the difference in the aromatic regions of the imidates and the quinazolinones appears to be the positive resonance effect caused by the overlap of an electron pair of the ethoxy group through the imidate double bond and the aromatic ring. The resonance effect seems to explain the shielding effect experienced by the proton on the adjacent ring position. Resonance of this type appears to be unlikely in the quinazolinones, since the N electron pair would exhibit amidic resonance into the carbonyl system. In this manner, the imino double bond acts as a deshielding group causing C_7H and C_8H to have nearly identical chemical shifts.

Experimental Section

Melting points were obtained on a Mel-temp capillary melting point apparatus and are reported uncorrected. Infrared spectra were obtained neat and in KBr on a Perkin-Elmer 281B spectrophotometer. ^{1}H NMR spectra were obtained neat, in $CDCl_3$, and in Me_2SO-d_6 with a Varian T-60 spectrometer. Combustion analyses were provided by M-H-W Laboratories, Phoenix, AZ.

Preparation of Methyl Anthranilate Esters 1. Ring opening of the requisite isatoic anhydride with excess absolute methanol in the presence of a catalytic amount of NaOH at reflux temperature yielded the corresponding anthranilate ester. Following reflux, the solution was filtered and then chilled in an ice bath. The product was collected on a filter, and the filtrate was then concentrated to give additional product. The combined solids were recrystallized from petroleum ether as colorless crystals.

Methyl 5-Chloroanthranilate (1b). According to the general procedure, 6-chloroisatoic anhydride (0.26 mol) and 1 g of NaOH in 100 mL of MeOH, heated at reflux for 20 h, yielded methyl 5-chloroanthranilate (76%): mp 69–70 °C (lit.[14] mp 69 °C).

Methyl 5-Bromoanthranilate (1c). According to the general procedure, 5-bromoisatoic anhydride[15] (0.15 mol) and 1 g of NaOH in 150 mL MeOH, heated at reflux for 3 h, gave methyl 5-bromoanthranilate in 89% yield: mp 68–69 °C (lit.[14] mp 74 °C).

Ethyl *N*-(2-Carbomethoxyphenyl)formimidate (3a)[3] and 3-(2-Carbomethoxyphenyl)-4(3*H*)-quinazolinone (4a). A mixture of 75.5 g (0.500 mol) of methyl anthranilate (**1a**) and 148 g (1.00 mol) of triethyl orthoformate (**2**, R = H) were heated at reflux temperature for 48 h. During this time the EtOH which had formed was removed via a Barrett trap. The excess orthoformate was distilled, leaving imidate **3a** and quinazolinone **4a**. The quinazolinone was collected on a filter and washed with Et_2O. Evaporation of the Et_2O gave an orange liquid, which was purified by distillation under reduced pressure. Pure formimidate **3a** was collected in 38.4% yield: bp 135–138 °C (6 mm). Spectral data matched that reported in the literature.[3]

The liquid which remained after distillation of **3a** crystallized upon cooling giving additional quinazolinone **4a**. The combined solids were recrystallized from 95% EtOH and gave 29.03 g (41.4%) of 3-(2-carbomethoxyphenyl)-4(3*H*)-quinazolinone: mp 174.5–175.0 °C (lit.[16] mp 171–172 °C; lit.[17] mp 173–174 °C).

A General Procedure for the Preparation of *N*-(2-Carbomethoxyphenyl) Imidate Esters 3. A solution of a methyl anthranilate (**1**) in an excess of orthoester **2** was stirred while heated at reflux temperature for a specific length of time. The solution was allowed to cool, and the excess orthoester and EtOH which had formed were removed by evaporation in vacuo. The orange-colored liquid which resulted was distilled under reduced pressure and the purity of each fraction was monitored by the disappearance of the amino N–H stretching bands and the appearance of the imino double bond vibration in the IR. A second distillation of those fractions that exhibited little or no N–H in their IR spectra yielded analytically pure imidate ester **3**.

Methyl *N*-(2-carbomethoxyphenyl)acetimidate (3b): IR (neat) 1740 (C=O), 1680 (C=N), 1235 and 1280 cm^{-1} (C–O); NMR (neat) δ 1.25 (t, 3, CH_2CH_3), 1.70 (s, 3, N=CCH_3), 3.70 (s, 3, OCH_3), 4.25 (q, 2, CH_2CH$_3$), 6.69 (dd, J = 2 and 8 Hz, 1, Ar H_6), 6.91 (td, J = 2 and 7 Hz, 1, Ar H_4), 7.31 (td, J = 2 and 7 Hz, 1, Ar H_5), 7.85 (dd, J = 2 and 8 Hz, 1, Ar H_3). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.30; H, 6.92; N, 6.51.

Methyl *N*-(2-carbomethoxyphenyl)propionimidate (3c): IR (neat) 1725 (C=O), 1680 (C=N), 1300 and 1240 cm^{-1} (C–O); NMR ($CDCl_3$) δ 1.00 (t, 3, N=CCH$_2$CH_3), 1.33 (t, 3, OCH$_2$CH_3), 2.08 (q, 2, N=CH_2CH$_3$), 3.73 (s, 3, OCH_3), 4.27 (q, 2, OCH_2CH$_3$), 6.72 (dd, J = 2 and 8 Hz, 1, Ar H_6), 6.97 (td, J = 2 and 7 Hz, 1, Ar H_4), 7.37 (td, J = 2 and 7 Hz, 1, Ar H_5), 7.83 (dd, J = 2 and 8 Hz, 1, Ar H_3). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.45; H, 7.41; N, 5.81.

Methyl *N*-(2-Carbomethoxy-4-chlorophenyl)formimidate (3d) and 3-(2-Carbomethoxy-4-chlorophenyl)-6-chloro-4-(3*H*)-quinazolinone (4d). To 2.40 mol of triethyl orthoformate at reflux temperature was added in two portions after 60 min 18.50 g (0.10 mol) of methyl 5-chloroanthranilate (**1b**). The reaction was heated for 72 h, and the excess triethyl orthoformate and EtOH were removed by distillation. Upon concentration to 100 mL turbidity resulted. After the mixture was allowed to stand overnight, the solid which had formed was collected on a filter and washed with Et_2O. Recrystallization from EtOH gave analytically pure quinazolinone **4d** (2.52 g, 14.5%): mp 173.5–174.0 °C; IR (KBr) 1730 (ester C=O), 1682 (C_4 C=O), 1610 (C=N), 1267 cm^{-1} (C–O); NMR ($CDCl_3$) δ 3.73 (s, 3, CH_3), 7.50–8.00 (m, 4, Ar H_7 and H_8 and Ar H_5' and H_6'), 8.20 (m, 3, C_2H, Ar H_5, and Ar H_3'). Anal. Calcd for $C_{16}H_{10}Cl_2N_2O_3$: C, 55.04; H, 2.89; N, 8.02. Found: C, 55.12; H, 3.09; N, 8.22.

The ether filtrate was concentrated, giving crude imidate ester. Formimidate **3d** was distilled under reduced pressure; 16.12 g (66.7%) pure **3d**, bp 128–132 °C (1.00 mm), was obtained. Analytically pure product was collected at bp 110–111 °C (0.45 mm): IR (neat) 1730 (C=O), 1650 (C=N), 1180, 1240, and 1290 cm^{-1} (C–O); NMR ($CDCl_3$) δ 1.35 (t, 3, CH_2CH_3), 3.78 (s, 3, OCH_3), 4.28 (q, 2, CH_2CH$_3$), 6.68 (d, J = 8 Hz, 1, Ar H_6), 7.22 (dd, J = 2 and 8 Hz, 1, Ar H_5), 7.45 (s, 1, N=CHOEt), 7.70 (d, J = 2 Hz, 1, Ar H_3). Anal. Calcd for $C_{11}H_{12}ClNO_3$: C, 54.67; H, 5.00; N, 5.80. Found: C, 54.43; H, 5.20; N, 5.75.

Methyl *N*-(2-carbomethoxy-4-chlorophenyl)acetimidate (3e): IR (neat) 1730 (C=O), 1675 (C=N), 1295, 1260, and 1220 cm^{-1} (C–O); NMR ($CDCl_3$) δ 1.33 (t, 3, CH_2CH_3), 1.77 (s, 3, C=NCH$_3$), 3.83 (s, 3, OCH_3), 4.30 (q, 2, CH_2CH$_3$), 6.75 (d, J = 8 Hz, 1, Ar H_6), 7.40 (dd, J = 2 and 8 Hz, 1, Ar H_5), 7.88 (d, J = 2 Hz,

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1, Ar H_3). Anal. calcd for $C_{12}H_{14}ClNO_3$: C, 56.37; H, 5.52; N, 5.48. Found: C, 56.29; H, 5.57; N, 5.66.

Methyl *N*-(2-carbomethoxy-4-chlorophenyl)propionimidate (3f): IR (neat) 1730 (C=O), 1677 (C=N), 1300, 1260, and 1230 cm^{-1} (C–O); NMR ($CDCl_3$) δ 1.02 (t, 3, N=CCH_2CH_3), 1.33 (t, 3, OCH_2CH_3), 1.75 (q, 2, N=CCH_2CH_3), 3.80 (s, 3, OCH_3), 4.25 (q, 2, OCH_2CH_3), 6.68 (d, J = 8 Hz, 1, Ar H_6), 7.32 (dd, J = 2 and 8 Hz, 1, Ar H_5), 7.83 (d, J = 2 Hz, 1, Ar H_3). Anal. Calcd for $C_{13}H_{16}ClNO_3$: C, 57.89; H, 5.98; N, 5.19. Found: C, 57.64; H, 5.77; N, 5.19.

Methyl *N*-(4-bromo-2-carbomethoxyphenyl)acetimidate (3g): IR (neat) 1732 (C=O), 1680 (C=N), 1295, 1264, and 1220 cm^{-1} (C–O); NMR ($CDCl_3$) δ 1.33 (t, 3, CH_2CH_3), 1.77 (s, 3, N=CCH_3), 3.82 (s, 3, OCH_3), 4.27 (q, 2, CH_2CH_3), 6.67 (d, J = 8 Hz, 1, Ar H_6), 7.47 (dd, J = 2 and 8 Hz, 1, Ar H_5), 8.00 (d, J = 2 Hz, 1, Ar H_3). Anal. Calcd for $C_{12}H_{14}BrNO_3$: C, 48.02; H, 4.70; N, 4.67. Found: C, 47.97; H, 4.58; N, 4.70.

Methyl *N*-(4-bromo-2-carbomethoxyphenyl)propionimidate (3h): IR (neat) 1730 (C=O), 1675 (C=N), 1300, 1264, and 1225 cm^{-1} (C–O); NMR ($CDCl_3$) δ 1.00 (t, 3, N=CCH_2CH_3), 1.33 (t, 3, OCH_2CH_3), 2.07 (q, 2, N=CCH_2CH_3), 3.77 (s, 3, OCH_3), 4.27 (q, 2, OCH_2CH_3), 6.61 (d, J = 8 Hz, 1, Ar H_6), 7.48 (dd, J = 2 and 8 Hz, 1, Ar H_5), 8.00 (d, J = 2 Hz, 1, Ar H_3). Anal. Calcd for $C_{13}H_{16}BrNO_3$: C, 49.70; H, 5.13; N, 4.46. Found: C, 49.59; H, 5.18; N, 4.47.

3-(2-Carbomethoxyphenyl)-2-methyl-4(3*H*)-quinazolinone (4b). Upon standing for approximately 15 months, a sample of **3b** gradually developed a quantity of crystalline material. Recrystallization of this solid from EtOH gave analytically pure 3-(2-carbomethoxyphenyl)-2-methyl-4(3*H*)-quinazolinone: mp 139–140 °C; IR (KBr) 1722 (ester C=O), 1690 (C_4 C=O), 1600 (C=N), 1280 cm^{-1} (C–O); NMR ($CDCl_3$) δ 2.10 (s, 3, C_2–CH_3), 3.67 (s, 3, OCH_3), 7.25–7.90 (m, 6, Ar H_6, H_7, and H_8 and Ar H_4', H_5', and H_6'), 8.10–8.25 (m, 2, Ar H_5 and Ar H_3'). Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.20; H, 4.89; N, 9.63.

3-(2-Carbomethoxyphenyl)-2-ethyl-4(3*H*)-quinazolinone (4c). Upon standing at ambient temperature for approximately 15 months, crystalline material gradually appeared in a sample of pure **3c**. The solid was recrystallized from EtOH, giving analytically pure quinazolinone **4c**: mp 146.5–147.0 °C; IR (KBr) 1720 (ester C=O), 1675 (C_4 C=O), 1600 (C=N), 1250 and 1270 cm^{-1} (C–O); NMR ($CDCl_3$) δ 1.23 (t, 3, CH_2CH_3), 2.41 (q, 2, CH_2CH_3), 3.67 (s, 3, OCH_3), 7.20–7.85 (m, 6, Ar H_6, H_7, and H_8 and Ar H_4', H_5', and H_6'), 8.20–8.40 (m, 2 Ar H_5 and Ar H_3'). Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.13; H, 5.26; N, 9.23.

A General Procedure for the Preparation of Unsubstituted and Substituted 3-Amino-4(3*H*)-quinazolinones 7. A mixture of 10–15 mmol of *N*-(2-carbomethoxyphenyl) imidate ester **3**, an excess (10–60%) of the requisite hydrazine, and 10 mL of 95% EtOH was stirred while being heated at reflux temperature. After the appropriate duration of reflux the reaction was allowed to cool. The product which had formed was collected on a filter and washed with a small amount of cold Et_2O. The filtrate was concentrated in vacuo, and the additional product was combined with the initial crop. Recrystallization from 95% EtOH gave pure crystalline quinazolinone **7**.

In the cases of those reactions that did not produce a precipitate, the solvent was evaporated in vacuo, and the product thus obtained was worked up in a manner similar to that described above.

3-Amino-4(3*H*)-quinazolinone (7a). Equimolar quantities (0.10 mol) of 99% hydrazine and imidate **3a** were mixed and vigorously stirred. The mixture was made homogeneous by addition of 5 mL of EtOH. Within a minute the reaction became very exothermic causing boiling of the solvent with subsequent precipitation of a yellow solid. After the mixture was sufficiently cooled in an ice bath, the product was collected on a filter. Recrystallization from EtOH gave 9.05 g (56.2%) of **7a** as fine colorless needles: mp 210–211 °C (lit.[18] mp 204 °C).

2-Ethyl-3-(methylamino)-4(3*H*)-quinazolinone (7e): IR (KBr) 3280 (N–H), 1660 (C=O), 1600 cm^{-1} (C=N); NMR ($CDCl_3$) δ 1.40 (t, 3, CH_2CH_3), 2.81 (d, 3, $NHCH_3$), 3.03 (q, 2, CH_2CH_3), 5.70 (q, 1, $NHCH_3$), 7.30–7.90 (m, 3, Ar H_6, H_7, and H_8), 8.23 (d, J = 8 Hz, 1, Ar H_5). Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 65.21; H, 6.43; N, 20.84.

6-Chloro-2-methyl-3-(methylamino)-4(3*H*)-quinazolinone (7f): IR (KBr) 3290 (N–H), 1660 (C=O), 1640 (C=N, shoulder), 1600 cm^{-1} (Ar C=C); NMR (Me_2SO-d_6) δ 2.60 (s, 3, C_2–CH_3), 2.77 (d, 3, $NHCH_3$), 6.33 (q, 1, $NHCH_3$), 7.40–8.10 (m, 3, Ar H_5, H_7, and H_8); mp 134.0–134.2 °C (lit.[11] mp 132–133 °C).

6-Chloro-2-methyl-3-(phenylamino)-4(3*H*)-quinazolinone (7g): IR (KBr) 3245 (N–H), 1680 (C=O), 1600 cm^{-1} (C=N); NMR (Me_2SO-d_6) δ 2.55 (s, 3, CH_3), 6.57–7.03 (m, 3, Ar H_2', H_4', and H_6'), 7.05–7.34 (m, 2, Ar H_3', and H_5'), 7.73 (m, 2, Ar H_7 and H_8), 8.00 (d, J = 2 Hz, 1, Ar H_5), 9.13 (s, 1, NH). Anal. Calcd for $C_{15}H_{12}ClN_3O$: C, 63.05; H, 4.23; N, 14.71. Found: C, 62.98; H, 4.38; N, 14.95.

6-Chloro-2-ethyl-3-(phenylamino)-4(3*H*)-quinazolinone (7h): IR (KBr) 3305 (N–H), 1675 (C=O), 1600 cm^{-1} (C=N); NMR (Me_2SO-d_6) 1.28 (t, 3, CH_2CH_3), 2.90 (q, 2, CH_2CH_3), 6.57–7.00 (m, 3, Ar H_2', H_4', and H_6'), 7.05–7.40 (m, 2, Ar H_3', and H_5'), 7.73 (m, 2, Ar H_7 and H_8), 8.07 (d, J = 2 Hz, 1, Ar H_5), 9.13 (s, 1, NH). Anal. Calcd for $C_{16}H_{14}ClN_3O$: C, 64.11; H, 4.71; N, 14.02. Found: C, 64.29; H, 4.84; N, 14.05.

6-Bromo-2-ethyl-3-(methylamino)-4(3*H*)-quinazolinone (7i): IR (KBr) 3290 (N–H), 1660 (C=O), 1610 (C=N, shoulder), 1600 cm^{-1} (Ar C=C); NMR (Me_2SO-d_6) δ 1.33 (t, 3, CH_2CH_3), 2.68 (d, 3, $NHCH_3$), 2.95 (q, 2, CH_2CH_3), 6.17 (q, 1, $NHCH_3$), 7.40 (d, J = 8 Hz, 1, Ar H_8), 7.73 (dd, J = 2 and 8 Hz, 1, Ar H_7), 8.07 (d, J = 2 Hz, 1, Ar H_5). Anal. Calcd for $C_{11}H_{12}BrN_3O$: C, 46.83; H, 4.29; N, 14.89. Found: C, 46.79; H, 4.41; N, 14.88.

6-Bromo-2-ethyl-3-(phenylamino)-4(3*H*)-quinazolinone (7j): IR (KBr) 3300 (N–H), 1670 (C=O), 1600 cm^{-1} (C=N); NMR (Me_2SO-d_6) δ 1.27 (t, 3, CH_2CH_3), 2.93 (q, 2, CH_2CH_3), 6.57–7.00 (m, 3, Ar H_2', H_4', and H_6'), 7.05–7.37 (m, 2, Ar H_3' and H_5'), 7.70 (d, J = 8 Hz, 1, Ar H_8), 7.97 (dd, J = 2 and 8 Hz, 1, Ar H_7), 8.18 (d, J = 2 Hz, 1, Ar H_5), 9.13 (s, 1, NH). Anal. Calcd for $C_{16}H_{14}BrN_3O$: C, 55.83; H, 4.10; N, 12.21. Found: C, 55.62; H, 4.25; N, 12.39.

3-Amino-2-ethyl-4(3*H*)-quinazolinone (7c): IR (KBr) 3320 and 3220 (N–H), 1680 (C=O), 1630 (C=N), 1600 cm^{-1} (Ar C=C); NMR ($CDCl_3$) δ 1.33 (t, 3, CH_3), 2.95 (q, 2, CH_2), 5.00 (s, exchangeable, 2, NH_2), 7.10–7.80 (m, 3, H_6, H_7, and H_8), 8.07 (dd, J = 8 and 2 Hz, 1, H_5); mp 122–123 °C (lit.[19] mp 152–153). Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.50; H, 5.88; N, 22.27.

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Registry No. **1a**, 134-20-3; **1b**, 5202-89-1; **1c**, 52727-57-8; **2a**, 122-51-0; **2b**, 78-39-7; **2c**, 115-80-0; **3a**, 59204-51-2; **3b**, 96999-04-1; **3c**, 96999-05-2; **3d**, 96999-06-3; **3e**, 96999-07-4; **3f**, 96999-08-5; **3g**, 96999-09-6; **3h**, 96999-10-9; **4a**, 51310-21-5; **4b**, 2006-80-6; **4c**, 94209-49-1; **4d**, 96999-11-0; **7a**, 14663-46-8; **7b**, 1898-06-2; **7c**, 50547-51-8; **7d**, 59169-44-7; **7e**, 96999-12-1; **7f**, 60512-89-2; **7g**, 1032-62-8; **7h**, 96999-13-2; **7i**, 96999-14-3; **7j**, 96999-15-4; $MeNHNH_2$, 60-34-4; $PhNHNh_2$, 100-63-0; NH_2NH_2, 302-01-2; 6-chloroisatoic anhydride, 4743-17-3; 5-bromoisatoic anhydride, 77603-45-3.

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