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THE PREPARATION OF AROMATIC AMIDINO ESTERS AND THEIR REACTION WITH PRIMARY AMINES

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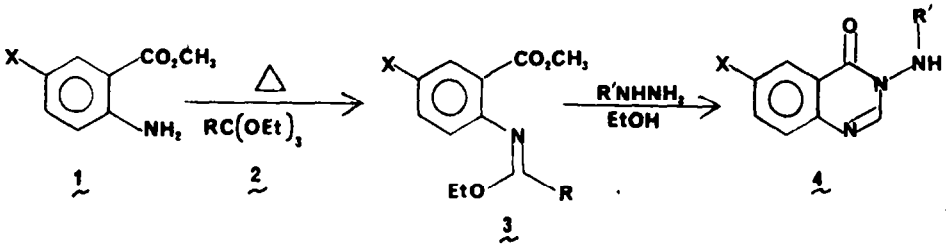
ABSTRACT: A series of aromatic amidino esters were prepared from the respective anthranilic acids by reaction with DMF acetal. These amidino esters were then condensed with a variety of primary amines to give the corresponding 3-substituted quinazolin-4-ones. Based on substituent effects, and the application of acid catalysis, a unifying mechanism is proposed.

Recently, Leiby[1] has shown that o-aminobenzoate esters can be condensed with ortho esters to give the corresponding imidate esters (Scheme 1).

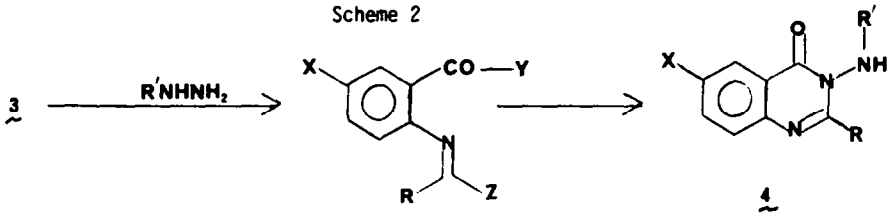
Scheme 1



1 2 3 4

These imidate esters (3) were then reacted with alkyl and aryl hydrazines to give the corresponding 3-amino-4(3H)-quinazolinones (4). Based on this work[1] and related work, Leiby suggested that the reaction was probably proceeding through an amidrazone (5) intermediate as opposed to an acylhydrazide (6) (Scheme 2).

Scheme 2



path a 6 Y = NHNHR', Z = OET
path b 5 Y = OCH_3, Z = NHNHR'

Our research group has developed[2] a convenient synthesis of 3-unsubstituted quinazolin-4-ones based on the reaction of anthranilic acids with Golds reagent. The reactivity of Gold's reagent has been found to be related[3] to the orthoamide $[HC(OCH_3)_2N(CH_3)_2]$ of formic acid. The chemistry of orthoamides and in particular DMF acetal has been reviewed[4] and a wide variety of useful synthetic applications have been reported for such reagents. We were particularly interested in a paper by Thenot and Horning[5] which described the reaction of α-amino acids with DMF acetal to give an amidino ester. Gschwend[6] and Fitt have recently begun to explore the synthetic applications of these amidino esters.

We, therefore, decided to look at the reaction of anthranilic acid and related compounds with DMF acetal in anticipation of concomitant functionalization of both the acid and the amino group to give the corresponding ortho amidino esters (See Table I).

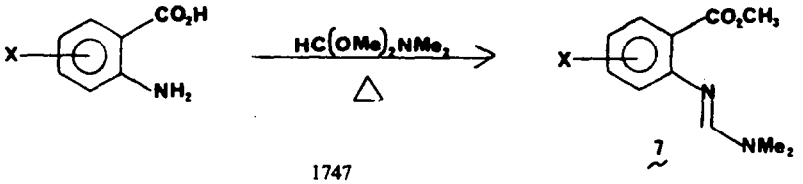


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Table I. Preparation of Aromatic Amidino Esters

Product Entry	X	% yield	bp or mp[a] (°C)
7a	H	95	90-100 (.2mm)[10]
7b	6-CH_3	81	95-105 (.2mm)
7c	5-CH_3	77	95-105 (.2mm)
7d	3-CH_3	72	83-95 (.3mm)
7e	4-Cl	94	95-105 (.2mm)
7f	5-Cl	98	79-84
7g	4-NO_2	99	89-94

[a] All compounds were purified by Kugelrohr distillation at reduced pressure and were found to be greater than 95% pure as determined by TLC analysis on silica gel 7GF with 75% hexane and 25% ethyl acetate as the eluant.

A variety of substituted anthranilic acids were reacted with excess DMF acetal in DMF solvent to give the respective amidino esters in good yield (72-99%). The presence of various electron withdrawing or releasing groups did not seem to adversely affect the efficiency of the reaction and the regiochemistry of the substituents did not seem to be crucial either. The resultant amidino esters were easily characterized by their 1720 cm^{-1} (O-C=O) and 1635 cm^{-1} (-N=C) absorptions in the IR and the six hydrogen singlet (-$N(CH_3)_2$) at 3.00 ppm and the three hydrogen singlet (-OCH_3) at 3.70 ppm in the ^1H NMR spectrum.

The next phase of our work involved the condensation of various primary amines with a representative aromatic amidino ester to determine if 3-N-substituted quinazolin-4-one formation was possible. Such substances have a history of significant biological activity[7] and the anticipated reaction would provide ready access to this class of compounds. The initial trials were carried out by refluxing the appropriate amidino ester with excess amine in the absence of any additional solvent. These results are reported in Table II.

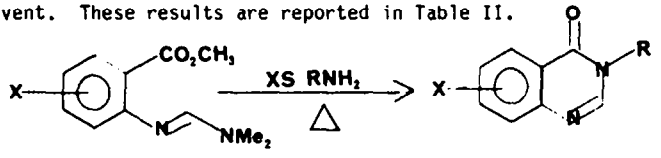

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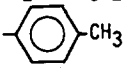
Table II. The Reaction of 5- and 6-Methyl Substituted Aromatic Amidino Esters With Primary Amines

Product Entry	X	R	% yield	bp or mp[a](°C)
8a	5-CH_3	-$(CH_2)_3CH_3$	100 (64)	98-99
8b	5-CH_3	-$(CH_2)_5CH_3$	100 (86)	30-32
8c	5-CH_3	-$CH(CH_3)CH_2CH_3$	99 (82)	65-68
8d	5-CH_3	-$CH_2CH(CH_3)_2$	(93)	57-60
8e	5-CH_3		nr	
8f	5-CH_3	-$C(CH_3)_3$	nr	
8g	6-CH_3	-$(CH_2)_3CH_3$	88 (43)	107-108
8h	6-CH_3	-$(CH_2)_5CH_3$	92 (83)	71-74
8i	6-CH_3	-$CH(CH_3)CH_2CH_3$	100	85-95
8j	6-CH_3	-$CH_2CH(CH_3)_2$	100	52-54

[a] Compounds were purified by recrystallization from a methanol-water mixture and were found to be greater than 95% pure as determined by TLC analysis on silica gel 7GF with hexane/ethyl acetate as the eluant. The yields in parenthesis refer to purified products.

The 5- and 6- methyl amidino esters were chosen for the initial feasibility studies due to the ease of interpretation of the ^1H NMR spectra. For the examples reported in Table II,

quinazolinone formation was efficient and complete for a variety amines with the exception of t-butylamine and p-toluidine. These examples were presumably less reactive due to a decrease in nucleophilicity for steric and electronic reasons, respectively. The characterization of the quinazolinones could be easily accomplished by examination of the IR[8] and ^{1}H NMR spectra. The IR spectra showed significant absorptions at 1665 cm^{-1} and 1630 cm^{-1} (-N-C=O). The ^{1}H NMR spectra of the quinazolinones showed marked changes in the aromatic region as compared to the starting amidino esters. These changes were consistent with Leiby's observations[1] for the analogous 3-amino systems and are representative of a greater degree of planarity in the heteroaromatic system which in turn produces enhanced deshielding. The disappearance of the $-OCH_3$ and the $-N(CH_3)_2$ groups at 3.70 ppm and 3.00 ppm, respectively, in the ^{1}H NMR spectra was observed in all cases.

Since the feasibility for this quinazolinone formation had been established in the case of a variety of non-sterically hindered aliphatic amines, we decided to turn our attention to the influence of aromatic substituent effects on the course of the ring closure. These results are reported in Table III.

^{1}H NMR analysis of the crude reaction mixtures indicated that 1) when there was no substituent on the aromatic ring or 2) when the substituent was electron withdrawing or 3) when the substituent was ortho to the amidine group, incomplete conversion was observed and this was usually accompanied by the formation of various side products. The 3-methyl substituted amidino ester showed no reactivity at all. The major by products (9 and 10) which were suggested by their IR and ^{1}H NMR spectra are depicted in Scheme 3.

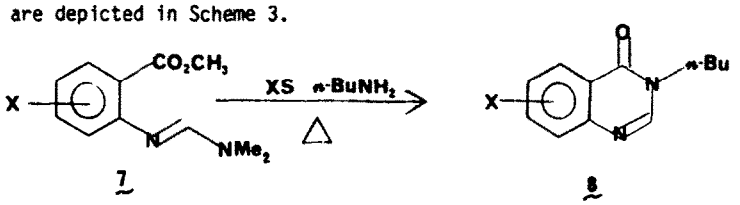


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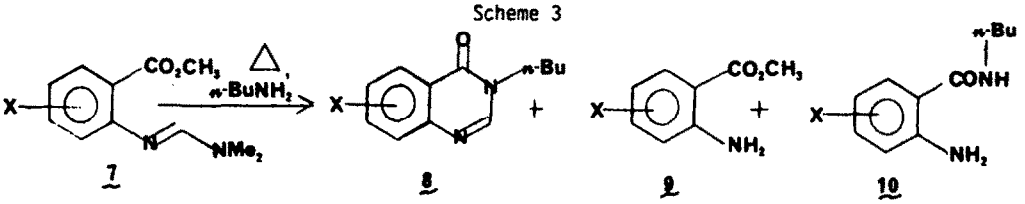
Table III. The Reaction of Various Substituted Aromatic Amidino Esters With n-Butylamine

Product Entry	X	% yield	bp or mp[a](°C)
8k	H	incomplete reaction	
8a	5-CH_3	100 (64)	98-99
8g	6-CH_3	88 (43)	107-108
8l	8-CH_3	nr	
8m	7-Cl	incomplete reaction	
8n	6-Cl	incomplete reaction	

[a] See footnote a Table II.

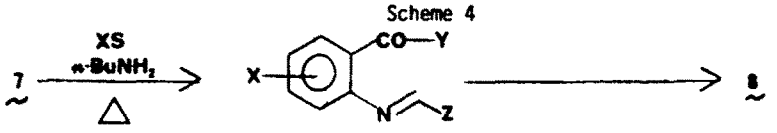
Scheme 3



7 8 9 10

These results suggest that the initial attack of the primary amine occurs at the amidine group and not at the ester group. This conclusion is consistent with Leiby's work[1] (Scheme 1) on imidate esters and also the dramatic lack of reactivity when a methyl group is ortho to the amidino group. Scheme 4 depicts the possible pathways with path b being favored over path a.

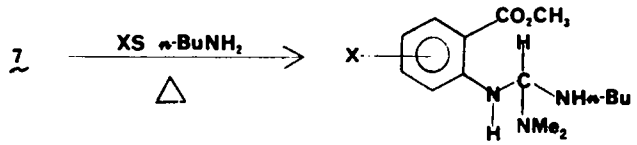
Scheme 4



path a 11 Y = NH-nBu, Z = NMe_2
path b 12 Y = OCH_3, Z = NHnBu

If path b is the favored route, an intermediate such as 13 could play an important role in the process.

Scheme 5



13

Depending on the relative basicities of the three amino groups of the proposed intermediate 13, one could form 12 or 9, during the elimination step. Electron withdrawing groups should favor the formation of 9 and electron releasing groups should favor the formation of 12. If this is true, then the application of acid catalysis should play an important role in this process in that if intermediate 13 were protonated at the more basic -NMe_2 group, it would become the best leaving group and intermediate 12 would be favored over the formation of 9. A variety of substituted amidino esters were then treated with 3-5 equivalents of various primary amines in dioxane with a catalytic amount of p-toluenesulfonic acid (Table IV).

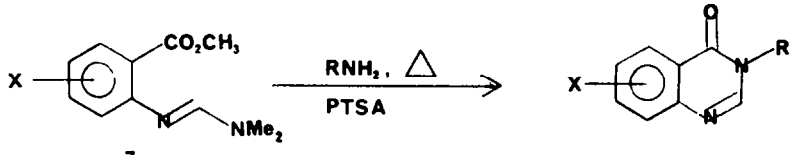


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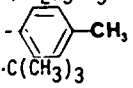
Table IV. The Reaction of Various Substituted Aromatic Amidino Esters With Primary Amines Under Acid Catalyzed Conditions

Product Entry	X	R	% yield	bp or mp[a] (°C)
8k	H	$-(CH_2)_3CH_3$	100 (61)	70-71
8l	8-CH_3	$-(CH_2)_3CH_3$	100 (43)	73-75
8m	7-Cl	$-(CH_2)_3CH_3$	100 (84)	88-89
8n	6-Cl	$-(CH_2)_3CH_3$	100 (77)	109-110
8o	5-CH_3		100 (36)	171-173
8p	H	$-C(CH_3)_3$	(25)	68-74
8q	6-CH_3	$-C(CH_3)_3$	34 (19)	121-125

[a] See footnote a Table II.

These reactions were followed by TLC analysis and were complete within 2 h without any indication of by-product formation. Not only did the reactions work well for the aromatic amidino esters which were ortho substituted or contained electron withdrawing groups, but the less reactive amines (p-toluidine and t-butylamine) also gave quinazolinone products. In the latter cases, the starting amidino esters are probably protonated at the imine nitrogen and are subsequently activated for nucleophilic attack. All these results seem to be consistent with path b of Scheme 4.

In conclusion, amidino esters can be easily prepared by reaction of the appropriately substituted anthranilic acid with excess DMF acetal in DMF solvent. These materials, which are easily distilled liquids, can be condensed with primary amines under acid catalyzed conditions to give quinazolin-4-ones in good yield and in high purity. Substituent effects point to the initial attack of the amine at the amidine site, followed by ring closure of the exchanged amidine to give the quinazolin-4-one. The overall process constitutes a mechanisticaly well defined, clean method for the synthesis of 3-N-substituted-quinazolin-4-ones.

Experimental Section[9]

The following procedures are typical of the experimental conditions used for the preparation of aromatic amidino esters, and 3-N-substituted-quinazolin-4-ones.

Methyl 2-(N,N-dimethyl-N'-formamidinyl)-5-methylbenzoate (7c):
A short path distillation apparatus was assembled complete with a thermometer, a drying tube and a magnetic stirrer. Into a 250 mL round bottomed flask was added 6.0 g (0.033 mol) of 5-methyl anthranilic acid, 11.8 g (0.088 mol) of dimethylformamide dimethylacetal and 30 mL of DMF. The flask was attached to the distillation apparatus and the mixture was heated to reflux. When the theoretical amount of methanol had distilled over the heat source was removed and the flask was allowed to cool to room temperature. The DMF and the residual DMF acetal were removed by Kugelrohr distillation at approximately 50°C (0.6 mm). The desired product was then distilled between 90 and 100°C (0.6 mm) to give 7.14g (98% yield) of a clear liquid: NMR ($CDCl_3$) δ 2.18 (s,3H), 2.86 (s,6H), 3.70 (s,3H), 6.58 (d, J=8Hz, 1H), 6.95 (d, J=8Hz, 1H), 7.11 (s,1H) and 7.33 (s,1H); IR (thin film) 1720, 1630, 1430, 1400, 1365, 880 and 820 cm^{-1}; mass spectrum, m/e 220 (M^+). Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C,65.42; H, 7.34; N, 12.72. Found: C, 64.75; H, 7.21; N, 12.44.

PTSA Catalyzed Preparation of 3-n-Butyl-8-methyl-quinazolin-4-one (8l):
A 250 mL three-necked round bottomed flask was equipped with a magnetic stirrer and a condenser. Into the flask was placed 1.0 g (0.0045 mol) of the 3-methylamidino ester, 1.33g (0.018 mol) of n-butylamine, 0.1g of p-toluene-sulfonic acid and 65 mL of 1,4-dioxane. The mixture was placed under a nitrogen atmosphere, refluxed for 4 h and followed by TLC. The dioxane was then removed in vacuo and the residue was dissolved in 65 ml of chloroform. The chloroform phase was washed with 5% aqueous sodium bicarbonate (3x30 ml) and water (3x30 ml). After drying over anhydrous magnesium sulfate the drying agent was removed by filtration and the solvent was removed in vacuo. The resulting crude product was recrystallized from a 1:1 methanol-water mixture to yield 0.83 g (85% yield) of a white solid: mp 73-75°C; NMR ($CDCl_3$) δ 0.91 (t, J=5Hz, 3H), 1.12-2.00 (m,4H), 2.52 (s,3H), 3.87 (t, J=6Hz, 2H), 7.10 (d, J=8Hz, 1H), 7.22-7.50 (m,1H), and 7.78-8.10 (m,2H); IR ($CHCl_3$) 1665, 1605, 720 and 660 cm^{-1}; mass spectrum, m/e 216 (M^+).

Methyl 2-(N,N-dimethyl-N'-formamidinyl)benzoate (7a):
bp 90-100°C (0.2mm); NMR ($CDCl_3$) δ 2.90 (s,6H), 3.70 (s,3H), 7.12 (s,1H), 6.56-7.32 (m,3H) and 7.52 (d of d, J=1Hz, J=6Hz, 1H); IR (thin film) 1720, 1635, 1440, 1400, 1365 and 760 cm^{-1}; mass spectrum, m/e 206 (M^+).
Methyl 2-(N,N-dimethyl-N'-formamidinyl)-6-methylbenzoate (7b):
bp 95-105°C (0.2 mm); NMR ($CDCl_3$) δ 2.17 (s,3H), 2.80 (s,6H), 3.71 (s,3H), 6.40-7.10 (m,3H), and 7.28 (s,1H); IR (thin film) 1725, 1630, 1430, 1400, 1365, 790 and 660 cm^{-1}; mass spectrum, m/e 220 (M^+).
Methyl 2-(N,N-dimethyl-N'-formamidinyl)-3-methylbenzoate (7d):
bp 83-95°C (0.2 mm); NMR ($CDCl_3$) δ 2.10 (s,3H), 2.90 (s,6H), 3.65 (s,3H), 6.70 (t, J=8Hz, 1H), 6.93 (s,1H), 7.05 (d, J=8Hz, 1H) and 7.40 (d, J=8Hz, 1H); IR (thin film) 1720, 1640, 1430, 1390, 1365, 780 and 760 cm^{-1}; mass spectrum, m/e 220 (M^+).
Methyl 4-Chloro-2-(N,N-dimethyl-N'-formamidinyl)benzoate (7e):
bp 95-105°C (0.2mm); NMR ($CDCl_3$) δ 2.90 (s,6H), 3.70 (s,3H), 6.70 (s,1H), 6.77 (d, J=8Hz, 1H), 7.17 (s,1H), and 7.50 (d, J=8Hz, 1H); IR (thin film) 1720, 1630, 1430, 1380, 920 and 875 cm^{-1}; mass spectrum, m/e 242, 240 (M^+). Anal. Calcd. for $C_{11}H_{13}N_2O_2Cl$: C, 54.88; H, 5.45; N, 11.64. Found: C, 53.50; H, 4.88; N, 10.96.
Methyl 5-Chloro-2-(N,N,-dimethyl-N'-formamidinyl)benzoate (7f):
mp 95-105°C; NMR ($CDCl_3$) δ 2.93 (s,6H), 3.73 (s,3H), 6.60 (d, J=8Hz, 1H), 7.00-7.27 (m,2H) and 7.50 (d, J=2Hz, 1H); IR ($CHCl_3$) 1715, 1635, 1430, 1390, 1365, 895 and 820 cm^{-1}; mass spectrum, m/e 242,240 (M^+).
Methyl 2-(N,N-dimethyl-N'-formamidinyl)-4-nitrobenzoate (7g):
mp 89-94°C; NMR ($CDCl_3$) δ 2.99 (s,6H), 3.80 (s,3H), 7.34 (s,1H) and 7.50-7.70 (m,3H); IR ($CHCl_3$) 1720, 1635, 1520, 1430, 1390, 1345, 895 and 820 cm^{-1};mass spectrum, m/e 251 (M^+).
3-n-Butyl-5-methylquinazolin-4-one (8a):
mp 98-99°C; NMR ($CDCl_3$) δ 0.93 (t, J=6Hz, 3H), 1.15-2.00 (m,4H), 2.80 (s,3H), 3.85 (t, J=6Hz, 2H), 6.92-7.46 (m,3H) and 7.78 (s,1H); IR ($CHCl_3$) 1665, 1630, 1610, 810 and 700 cm^{-1}; mass spectrum, m/e 216 (M^+).
3-n-Hexyl-5-methylquinazolin-4-one (8b):
mp 30-32°C; NMR ($CDCl_3$) δ 0.90 (t, J=4Hz, 3H), 1.12-2.00 (m,8H), 2.88 (s,3H), 3.89 (t, J=6Hz, 2H), 7.00-7.56 (m,3H) and 7.86 (s,1H); IR ($CHCl_3$) 1665, 1610, 810 and 700 cm^{-1}; mass spectrum, m/e 244 (M^+).
3-s-Butyl-5-methylquinazolin-4-one (8c):
mp 65-68°C; NMR ($CDCl_3$) δ 0.90 (t, J=6Hz, 3H), 1.40 (d, J=6Hz, 3H), 1.52-2.00 (m,2H), 2.80 (s,3H), 4.80 (hex, J=6Hz, 1H), 6.91-7.48 (m, 3H) and 7.78 (s,1H); IR ($CHCl_3$) 1665, 1610, 810 and 700 cm^{-1}; mass spectrum, m/e 216 (M^+).
3-i-Butyl-5-methylquinazolin-4-one (8d):
mp 57-60°C; NMR ($CDCl_3$) δ 0.94 (d, J=6Hz, 6H), 1.95-2.40 (m,1H), 2.80 (s,3H), 3.65 (d, J=6Hz, 2H), 6.92-7.50 (m,3H), and 7.73 (s,1H); IR ($CHCl_3$) 1665, 1610, 810 and 700 cm^{-1}; mass spectrum, m/e 216 (M^+).

3-n-Butyl-6-methylquinazolin-4-one (8g):
mp 107-108°C; NMR ($CDCl_3$) δ 0.92 (t, J=6Hz, 3H), 1.15-2.00 (m,4H), 2.40 (s,3H), 3.88 (t, J=6Hz, 2H), 7.35 (broad s, 2H), 7.75 (s,1H) and 7.90 (s,1H); IR ($CHCl_3$) 1635, 1605, 900 and 830 cm^{-1}; mass spectrum, m/e 216 (M^+). Anal Calcd. for $C_{13}H_{16}N_2O$: C, 72.18; H, 7.47; N, 12.95. Found: C, 71.90; H, 7.38; N, 12.83.

3-n-Hexyl-6-methylquinazolin-4-one (8h):
mp 71-74°C; NMR ($CDCl_3$) δ 0.88 (t, J=4Hz, 3H) 1.10-2.00 (m, 8H), 2.40 (s,3H), 3.90 (t, J=6Hz, 2H), 7.40 (broad s, 2H), 7.80 (s,1H) and 7.93 (s,1H); IR ($CHCl_3$) 1665, 1605, 910 and 830 cm^{-1}; mass spectrum, m/e 244 (M^+).

3-s-Butyl-6-methylquinazolin-4-one (8i):
mp 85-95°C; NMR ($CDCl_3$) δ 0.90 (t, J=6Hz, 3H), 1.41 (d, J=6Hz, 3H), 1.55-2.08 (m,2H), 2.42 (s,3H), 4.88 (hex, J=6Hz, 1H), 7.42 (broad s, 2H), 7.82 (s,1H) and 7.92 (s,1H); IR ($CHCl_3$) 1665, 1620, 1605, 910 and 830 cm^{-1}; mass spectrum, m/e 216 (M^+).

3-i-Butyl-6-methylquinazolin-4-one (8j):
mp 52-54°C; NMR ($CDCl_3$) δ 0.93 (d, J=6Hz, 6H), 1.90-2.40 (m,1H), 2.43 (s,3H), 3.71 (d, J=6Hz, 2H), 7.41 (broad s, 2H), 7.76 (s, 1H) and 7.94 (s, 1H). IR ($CHCl_3$) 1665, 1620, 1605, 910 and 830 cm^{-1}; mass spectrum, m/e 216 (M^+).

3-n-Butylquinazolin-4-one (8k):
mp 70-71°C; NMR ($CDCl_3$) δ 0.98 (t, J=6Hz, 3H), 1.15-2.00 (m, 4H), 3.95 (t, J=6Hz, 2H), 7.10-7.64 (m,3H), 7.87 (s,1H) and 8.10 (d, J=8Hz, 1H); IR ($CHCl_3$) 1665, 1610 and 700 cm^{-1}; mass spectrum, m/e 202 (M^+).

3-n-Butyl-7-chloroquinazolin-4-one (8m):
mp 88-89°C; NMR ($CDCl_3$) δ 0.95 (t, J=6Hz, 3H), 1.16-2.00 (m,4H), 3.90 (t, J=6Hz, 2H), 7.25 (d of d, J=2Hz, J=8Hz, 1H), 7.50 (d, J=2Hz, 1H), 7.88 (s,1H) and 8.04 (d, J=8Hz, 1H); IR ($CHCl_3$) 1675, 1605, 905 and 820 cm^{-1}; mass spectrum, m/e 238, 236 (M^+). Anal. Calcd. for $C_{12}H_{13}N_2OCl$: C, 60.88; H, 5.55; N, 11.84. Found C, 60.62; H, 5.37; N, 11.75.

3-n-Butyl-6-Chloroquinazlin-4-one (8n):
mp 109-110°C; NMR ($CDCl_3$) δ 0.93 (t, J=6Hz,3H), 1.11-2.00 (m,4H), 3.90 (t, J=6Hz, 2H), 7.48 (broad s, 2H), 7.82 (s, 1H) and 8.00 (s,1H); IR ($CHCl_3$) 1670, 1605, 905 and 835 cm^{-1}; mass spectrum, m/e 238,236 (M^+).

5-Methyl-3-(p-methylphenyl)quinazolin-4-one (8o):
mp 171-173°C; NMR ($CDCl_3$) δ 2.36 (s,3H), 2.80 (s,3H), 7.13 (broad s, 5H), 7.31-7.55 (m,2H) and 7.88 (s,1H); IR ($CHCl_3$) 1675, 1615, 810 and 700 cm^{-1}; mass spectrum, m/e 250 (M^+).

3-t-Butylquinazolin-4-one (8p):
mp 68-74°C; NMR ($CDCl_3$) δ 1.73 (s,9H), 7.08-7.63 (m,3H) and 8.02-8.28 (m,2H); IR ($CHCl_3$) 1670, 1605, 1395, 1370 and 700 cm^{-1}; mass spectrum, m/e 202 (M^+).

3-t-Butyl-6-methylquinazolin-4-one (8q):
mp 121-125°C; NMR ($CDCl_3$) δ 1.70 (s,9H),2.30 (s,3H), 7.35 (broad s, 2H), 7.88 (s,1H) and 8.07 (s,1H); IR ($CHCl_3$) 1665, 1615, 1415, 1390, 910 and 830 cm^{-1}; mass spectrum, m/e 216 (M^+).

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References and Notes

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9. Infrared spectra were recorded on either a Perkin-Elmer Model 1420 infrared spectrometer as thin films or nujol mulls. NMR spectra were obtained in CCl_4, $DCCl_3$, or Me_2SO - d_6 solutions , $(CH_3)_4$ Si internal standard , at 60 MHz with a Varian EM-360 spectrometer. All boiling points and melting points are uncorrected and melting points were recorded on a Fisher-Johns melting-point apparatus. Elemental analyses were carried out by Robertson Laboratory, Inc. of Florham Park, NJ.
10. This compound has been previously reported in a Hungarian patent. See Chem. Abst., 1971, 74, 141854W.