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Synthesis of Chrysogine, a Metabolite of *Penicillium chrysogenum* and some related 2-substituted 4-(3H)-Quinazolinones

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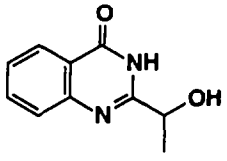
Summary Syntheses of both enantiomers of chrysogine, 2-(α-hydroxyethyl)-4(3H)-quinazolinone, **1** from 2-aminobenzamide are reported. Thus reaction of 2-aminobenzamide and optically active α-acetoxypropionyl chloride gave **9**, which upon saponification and cyclization induced by aqueous sodium carbonate at room temperature gave chrysogine. The enantiomeric purity of **1** was determined by NMR. Inversion of (-)-(S)-**1**, using the Mitsunobo reaction, gave (+)-(R)-**1**. Reduction of 2-acetyl-4(3H)-quinazolinone **2** with baker's yeast gave the S-enantiomer of **1**. The cyclization method used could be extended and a number of 2-(α-hydroxy)alkyl-4-(3H)-quinazolinones are also reported.

Introduction

The mold metabolite chrysogine (**1**) was isolated in 1973 from strains of *Penicillium chrysogenum*[1] and *Alternaria citri*[2]. Related secondary metabolites such as 2-acetyl-4(3H)-quinazolinone (**2**) and 2-pyruvoylaminobenzamide (**3**) have also been isolated, the former from *Fusarium culmorum*[3], and *Alternaria citri*[2] and the latter from *Penicillium chrysogenum*[4], and *Colletotrichum lagenarium*[5].



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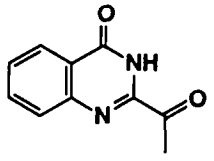

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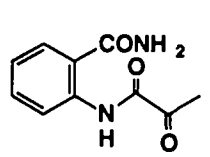

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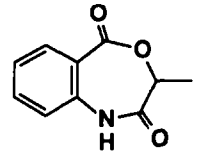

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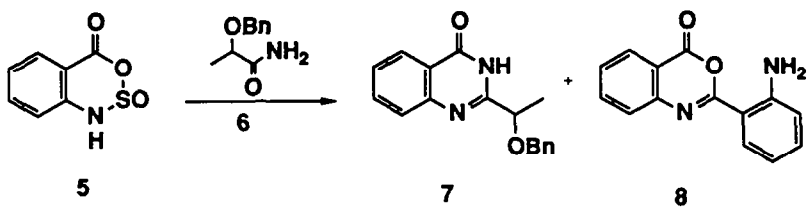
These metabolites are obvious starting materials in the synthesis of chrysogine and several transformations between them and 2-(α-hydroxyethyl)-4(3H)-quinazolinone (**1**) has been reported[4]. Already in 1964 Uskokovic[6] prepared racemic **1** by conversion of *N*–(α–bromopropionyl)-anthranilic acid to 3-methyl-4,1-benzoxazepin-2,5(1H,3H)-dione (**4**), which was subsequently ring-contracted with anhydrous ammonia in methanol. Another synthesis is due to Kametani[7], who treated the unstable sulphinamide anhydride **5**, prepared from anthranilic acid,

with *O*-benzyllactamide (**6**) and obtained (after chromatography) racemic *O*-benzylchrysogine (**7**) together with the benzoxazinone **8** (Scheme 1). Finally, debenzylation of **7** in refluxing HCl in ethanol gave racemic chrysogine. The total yield in this sequence was 30 %.

In this paper we describe convenient preparations of both racemic and optically active chrysogine.



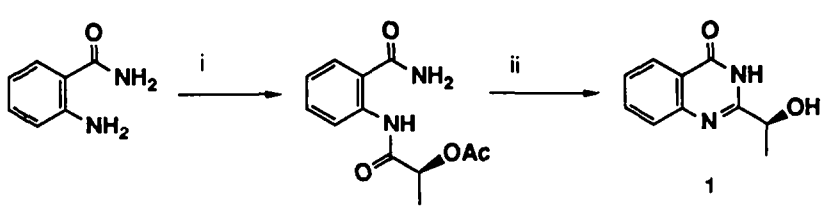
5 7 8

Scheme1

Results and discussion

We have accomplished the preparation of chrysogine by condensing 2-aminobenzamide with optically active α–acetoxypropionyl chloride[8] (obtained from L-lactic acid, which in turn establishes the absolute configuration of chrysogine as (-)-(S)-2-(α-hydroxyethyl)-4(3H)-quinazolinone).

The reaction (Scheme 2) is conveniently completed in one pot but the intermediate **9** can be isolated in 76% yield. Ring closure of **9** and subsequent saponification by aqueous sodium carbonate at room temperature gave chrysogine **1**(75%) with an optical activity of $[\alpha]_D$ -41. This optical activity is higher than that ($[\alpha]_D$ -26±4) reported by Hikino[1].



i = α-acetoxypropionyl chloride **9**
ii = Na_2CO_3(aq)

Scheme 2

In order to explain this difference in optical activity we tried to racemize chrysogine under basic conditions (2M NaOH, 7d, 25°C). However, no racemization was detected. Hence, it is difficult to explain why natural chrysogine is partly racemic, and this renders reisolation of **1**

from *Penicillium chrysogenum* under strictly controlled conditions highly desirable.

Reduction of 2-acetyl-4(3H)-quinazolinone (2) with baker's yeast[9] resulted in (-)-(S)-1 ($[\alpha]_D$ –36). This result is in consonance with Prelog's rule[10] which states that reduction of a methyl ketone with baker's yeast should give the S–alcohol. After the completion of our work a number of heteroaromatic ketones have, with various success, been reduced[11] with baker's yeast. Thus *e.g.* 2–acetylpyridine gave 2–(α–hydroxyethyl)pyridine in an optical yield of 96 % ee (S–configuration), whereas reduction of 2–acetylfurane and 2–acetylthiophene gave the corresponding alcohols with low optical purity (0 and 15% ee).

The optical purity of **1** was determined[12] by NMR as follows; racemic chrysogine was reacted with (+)-(S)–α–methoxy-α-trifluoromethylphenylacetyl chloride[12] (MTPA-Cl) to give a pair of diastereomers (**10a** and **10b**). In the ^{1}H-NMR spectrum the methyl peaks of **10a** and **10b** are separated by 0.06 ppm.

When (-)-(S)-1 ($[\alpha]_D$ -41) was allowed to react in the same manner only one of the diastereomers (**10b**) could be observed and the optical purity was accordingly determined to >98% ee(Fig. 1).

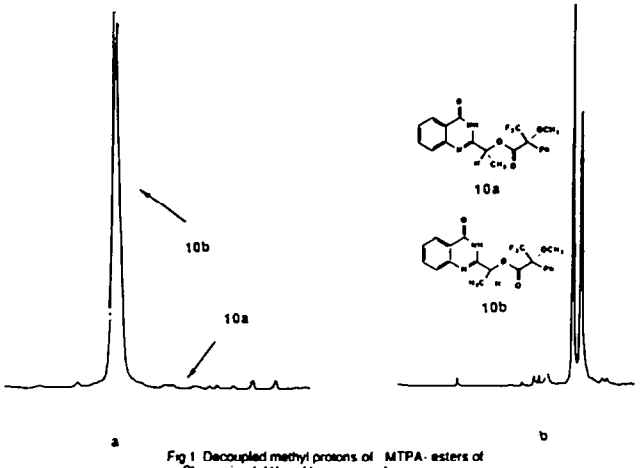


Fig 1 Decoupled methyl protons of MTPA- esters of a Chrysogine (-41) and b. racemic chrysogine

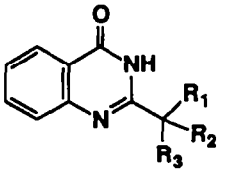
The antipode of chrysogine, (+)–(R)–1, could be prepared either from 2–aminobenzamide and (S)–α–chloropropionyl chloride[13] giving ($[\alpha]_D$ +20) or better by inversion of (-)–(S)–1 ($[\alpha]_D$ -40) *via* the Mitsunobo reaction[14] giving (+)–(R)–1 ($[\alpha]_D$ +37).

By similar methods the related (S)–2–(α–bromoethyl)-4(3H)–quinazolinone ($[\alpha]_D$ –50)(11) and (S)–2–(α–chloroethyl)-4(3H)–quinazolinone ($[\alpha]_D$ +22)(12) were obtained in reasonable yields starting from L–alanine and 2–aminobenzamide.

In addition racemic chrysogine could conveniently be synthesized from 2–(α–bromo-

propionylamino)benzamide **13** by treatment with base (OH^-, H_2O) (Scheme 3).The intermediate, racemic **11**, was readily obtained by mild cyclization of **13**. In addition a number of related 2-substituted quinazolinones were similarly synthesized by this method (Table 1).

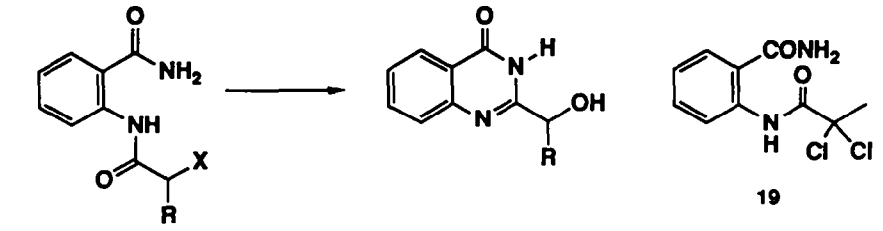
TABLE 1



	R_1	R_2	R_3	yield(%)	m.p.(°C)	m.p.(lit.)
11	Br	CH_3	H	92	234 dec	
1	OH	CH_3	H	76	190-92	189-91[1]
25	OH	CH_3	CH_3	60	150-51	147-8[17]
15	OH	C_6H_5	H	86	208	218[16]
16	OEt	C_6H_5	H	68	142-44	
17	OH	H	H	81	215	214[35]
26	OAc	H	H	87	196-97	196-97[34]
27	OAc	C_6H_5	H	97	177	173[16]
28	N_3	CH_3	H	72	156	
29	OH	$CH_2CH(CH_3)_2$	H	65	142-44	
30	NH_2	CH_3	H	70	192-94	
22	$NHCOCF_3$	CH_3	H	90	272-275	
18	Br	H	H	90	>300	>300[37]
12	Cl	CH_3	H	95	220dec	

However, attempts to cyclize 2–(α–chlorophenacyl)aminobenzamide **14** to 2–(α–chlorobenzyl)-4(3H)–quinazolinone failed. No reaction took place when **14** was refluxed in toluene with *p*-toluenesulphonic acid as catalyst and when **14** was treated with base, either (OH^-, H_2O) or (Na_2CO_3,$EtOH/H_2O$), the cyclization was followed by rapid nucleophilic displacement of chlorine to give 2–(α–hydroxybenzyl)-4(3H)–quinazolinone **15** and 2–(α–ethoxybenzyl)-4(3H)–quinazolinone **16**, respectively.

In connection with these studies we found that acetoxyacetic anhydride readily reacted with 2-aminobenzamide to give 2–acetoxymethyl-4(3H)–quinazolinone, which upon treatment with sodium hydroxide (2M) at 80°C gave 2–hydroxymethyl-4(3H)–quinazolinone (**17**) in 81% yield. Compound **17** is also available by hydrolysis of 2–bromomethyl-4(3H)–quinazolinone **18**, readily prepared by bromination of 2–methyl-4(3H)–quinazolinone with NBS in DMF. Similar brominations of 2-ethyl-4(3H)–quinazolinone were difficult to drive to completion.



13 R = CH_3, X = Br
14 R = Ph, X = Cl

1 R = CH_3
15 R = Ph

Scheme 3

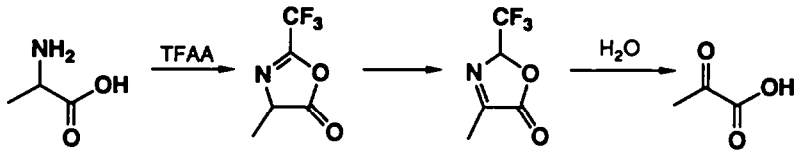
Reactive derivatives of S–mandelic acid behaved similarly as the corresponding derivatives of S–lactic acid. Thus *O*–acetylmandelic anhydride and 2–aminobenzamide could be converted to 2–(α–hydroxybenzyl)-4(3H)–quinazolinone **15** in an ee of 80%. Although a likely candidate, **15** has not yet been identified as a natural product. Racemic **15** could readily be obtained by reduction of the known 2–benzoyl-4(3H)–quinazolinone[15-19] with sodium borohydride. This ketone was more easily prepared by base-induced cyclization of 2–(phenylglyoxylyl)-aminobenzamide as described above. Bromination, followed by hydrolysis, of 2–benzyl-4(3H)–quinazolinone (a natural product known as glycosminine) was also found to be a feasible route to racemic **15**. The TMEDA catalyzed condensation[20] of phenylacetamide with isatoic anhydride was found to be more convenient than previously published routes[19,21-23] to glycosminine.

2–Acetyl-4(3H)–quinazolinone (**2**) was easily prepared from 2–aminobenzamide, which when treated with α,α–dichloropropionic anhydride (prepared from commercially available sodium α,α–dichloropropionate and thionyl chloride[24]) gives **19**. The subsequent cyclization and hydrolysis to **2** was accomplished by treatment with aqueous sodium hydroxide. The previous preparation[4], described by Suter and Turner, which was claimed to involve pyruvoyl chloride (prepared from pyruvic acid and thionyl chloride[24]) was repeated. As it is known[25,26] that this operation gives a complex mixture containing α,α–dichloropropionyl chloride as the main product it came as no surprise that **19** is an intermediate in this preparation.

Chrysogine could be converted to **2** by a Swern oxidation. Attempted direct oxidation[27] of 2–ethyl-4(3H)–quinazolinone with ammonium persulphate in the presence of Ag^+ failed and oxidation with SeO_2 (*c.f.* ref 15) gave complex mixtures.

As it is known[28] that 4–methyl-2–trifluoromethyl-5(2H)–oxazolone (**20b**) can be hydrolyzed to pyruvic acid we tried the interaction of **20b** with 2–aminobenzamide as a possible alternative

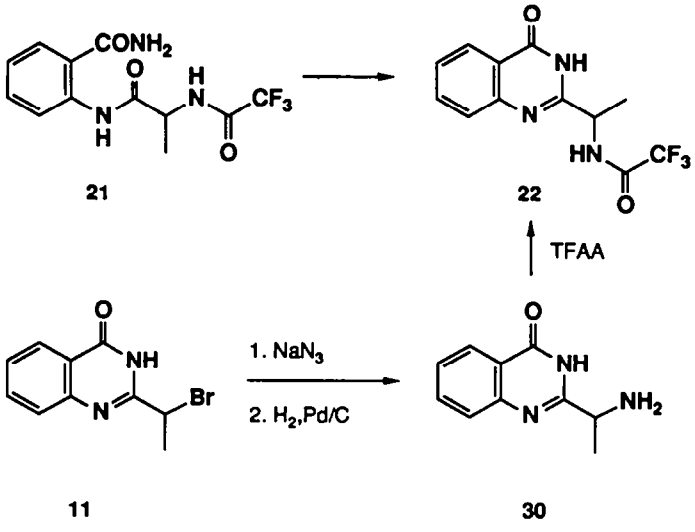
approach to **2**. The 5(2H)–oxazolone **20b** is readily obtained from trifluoroacetic anhydride and alanine. The 5(4H)–oxazolone **20a**, initially formed, rapidly rearranges to **20b**.(Scheme 4)



20a **20b**

Scheme 4

In the reaction between 2–aminobenzamide and **20b**, the initial attack by the amino group on **20b** resulted in ring opening and rapid isomerization to 2–(*N*-trifluoroacetyl-1-aminopropionyl) aminobenzamide (**21**). Final ring closure gave 2–(α–(*N*–trifluoroacetyl))aminoethyl)-4(3H)–quinazolinone (**22**) which also was synthesized from **11** as outlined in Scheme 5.



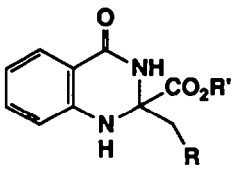
21 **22**

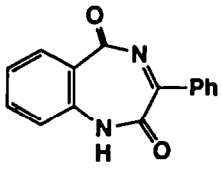
11 **30**

Scheme 5

The interactions, under various conditions, of 2–aminobenzamide and some α–keto acids esters were also studied. In all cases compounds of the type **23** were obtained, which is not unexpected since Rhee and White[21] already have reported that phenylpyruvic acid and 2–amino-benzamide yielded **23d**. Attempted ring-expansion (induced by diphenylphosphoryl azide) of compounds **23d** and **23e** to benzodiazepin-2,5–diones failed as the COOH group was eliminated

giving 2–benzyl- and 2–ethyl-4(3H)–quinazolinone , respectively. However, cyclization of 2–phenylglyoxylyl aminobenzamide in a basic medium (2M KOH, 60°C, 1h) gave a mixture (2:1) of 2–benzoyl-4(3H)–quinazolinone and 3–phenyl-1,4(1H)–benzodiazepin-2,5–dione **24**. At higher temperature (100°C) this cyclization only gave 2–benzoyl-4(3H)–quinazolinone.





23 a R = R' =H
b R = H, R' = CH_3
c R = R' = CH_3
d R = Ph, R' = H
e R = CH_3, R' =H

24

EXPERIMENTAL

All melting points are uncorrected, IR-spectra (KBr-discs) were obtained by using a Perkin-Elmer 257 instrument. NMR-spectra were recorded on a Varian EM-360 instrument ($CDCl_3$ or $DMSO_{d6}$ as solvents and TMS as internal standard). Mass spectra were obtained with an LKB 9000 (70eV) mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

O-Acetylmandelic acid anhydride

Acetic anhydride (25 ml) was added to mandelic acid (3.04 g, 0.02 mol) and the mixture was heated to 150 °C. The acetic acid formed and the excess acetic anhydride was distilled off. The remaining acetic anhydride was removed by distillation at low pressure (0.05 mm Hg, 50 °C) for 1h. The crude product (65 %) was used directly. m.p. 61-63 °C ($[\alpha]_D$+150 (c 2.5 in EtOH)). δ_H 6.9 (5H, m, ar), 5.6 (1H, s, CH), and 1.6 (3H, s, OCH_3).

α-Acetoxypropionyl chloride

O-Acetyllactic acid[29] (6g, 45mmol) was dissolved in dry benzene (25ml), whereupon oxalyl chloride (4.3 ml, 49 mmol) was added followed by 1 drop of dry DMF. The solution was stirred over night at ambient temperature, the solvent was evaporated and the residue distilled to give α-acetoxypropionyl chloride (4g, 52%), b.p.60-64 °C (20 mmHg) $[\alpha]_D$-34.7 (neat) (lit.[8] b.p. 51–53°C (11 mmHg)).

α,α-Dichloropropionic anhydride

Thionyl chloride (50ml) was added to a solution of the sodium salt of α,α-dichloropropionic acid (82g) in CH_2Cl_2 (150ml). After a reflux period of 2h the mixture was distilled (b.p. 70–73°C(11mmHg)) to give (29g, 43%) (lit.[24] b.p. 196-200 °C).

(-)-(S)-α-Chloropropanoic acid and (-)-(S)-α-Bromopropanoic acid

These acids were prepared from L-alanine as described by Koppenhoefer and Schurig[13].

(-)-(S)-α-Bromopropionyl chloride

From (-)-(S)-α-bromopropanoic acid and oxalyl chloride as described above for α–acetoxypropionyl chloride. Yield: 63 % ($[\alpha]_D$-27.4 (neat)) (lit. [30]-27.1(neat)).

(-)-(S)-α-Chloropropionyl chloride

Yield: 43% ($[\alpha]_D$+5.5 (neat)) (lit.[31] $[\alpha]_D$ +4.6 (neat)).

2-(α–Acetoxypropionyl)aminobenzamide 9

2-Aminobenzamide (1.36g, 10mmol) was dissolved in dry dioxane (20ml), α–acetoxypropionyl chloride (2.46g, 10mmol) was added and the mixture was stirred at ambient temperature (14h). The mixture was poured into cold water, neutralized with $NaHCO_3$ (aq,10%), and extracted with EtOAc. The organic phase was dried and evaporated to give **9** (1.9g, 76%), m.p. 135°C (from EtOAc) ($[\alpha]_D$ -103.4 (c 1 in EtOH)) (lit.[4] m.p. 134-135°C). ν_{max} 3360, 3180, 1750, 1670, 1635, and 1520 cm^{-1}. δ_H 11.8 (1H, br, NH), 8.6 (1 H, d, , ar), 7.6-6.9 (3 H, m, ar), 6.3 (2 H, br, NH), 5.3 (1 H, q, CH), 2.2 (3 H, s, CH_3), and 1.55 (3 H, d, CH_3).

2-(α-Acetoxyacetyl)aminobenzamide

A solution of 2-aminobenzamide (2.72 g, 20 mmol) and acetoxyacetic anhydride[32] (4.36 g, 20mmol) in dioxane (100 ml) was stirred for 1 h at ambient temperature and then poured into water, yield 3.35 g (75%), m.p. 182-184°C. m/z 236 (M+), 218, 177, 176, 175, 163, 146, 134, 119, 92, and 90.

2-(α-Acetoxybenzoyl)aminobenzamide

This reaction gave a mixture of 2-(α-acetoxybenzyl)aminobenzamide and **27**. **27** precipitated directly, the mother liquor was neutralized and was extracted with EtOAc. The organic phase was dried ($MgSO_4$) and evaporated. The residue was flashchromatographed to give 2-(α-acetoxybenzoyl)amino benzamide (35%), m.p. 285-287 °C. ν_{max} 3420, 3380, 1740, 1670, 1620, and 1520 cm-1. δ_H 12.7 (1 H, s, NH), 8.4 (1 H, d, ar), 8.3 (1 H, s, NH), 7.8 (2 H,br d, ar+NH), 7.5-7.4 (6 H,m, ar), 7.1 (1 H, m, ar), 6.0 (1 H, s, CH),and 2.2 (3 H,s, CH_3)

2-(α-Bromopropionyl)aminobenzamide 13

α-Bromopropionyl chloride (3.4g, 20mmol) was added dropwise to a cold solution (icebath) of 2–aminobenzamide (2.7g, 20mmol) in CH_2Cl_2 (50ml) and pyridine (4ml). The reaction mixture was stirred at ambient temperature for 10h. The solvent was evaporated, H_2O/EtOH was added and pH adjusted to 6-7. The precipitate was collected and recrystallized to give **13** (4.5g, 84 %), m.p. 145–147 °C(EtOH). ν_{max} 3380, 3190, 1670, and 1510 cm^{-1}. δ_H 12.2 (1 H, s, NH), 8.4 (1 H, d, ar), 8.3, (1 H, br s, NH), 7.8 (2 H, br d, ar+NH), 7.5 (1 H, m, ar), 7.2 (1 H, m, ar), 4.8 (1 H, q, CH), and 1.7 (3 H, d, CH_3).

The following compounds were similarly prepared:

2-(α,α-Dichloropropionyl)aminobenzamide 19

Yield: 85 %, m.p. 181-182 °C. δ_H 11.8 (1 H, br, NH), 8.4 (2 H, br d, ar+ NH), 7.9 (2 H, br d, ar+ NH), 7.6 (1 H, m, ar), 7.2 (1 H, m, ar), and 2.4 (3 H, s, CH_3); ν_{max} 3400, 3180, 1670, 1620, 1585, 1515, 1385, 1300, and 780 cm^{-1}. (Found: C, 46.5; H, 3.9; N, 10.2; Cl, 26.5.$C_{10}H_{10}Cl_2N_2O_2$requires C, 46.0; H, 3.8; N, 10.7; Cl, 27.2 %.)

2-(α-Chloropropionyl)aminobenzamide

Yield: 44%, m. p. 148-149°C($[\alpha]_D$ -105 (c 1 in EtOH)). ν_{max} 3372, 3202, 1687, 1658, 1610, 1588, 1520, 1450, 1396, 766, and 755 cm^{-1}. δ_H 12.0 (1H, s, NH), 8.6 (1H, dd, ar), 7.5 (2H, m, ar), 7.1 (1H, m, ar), 6.5- 5.5 (2H, br, NH_2), 4.5 (1H, q, CHCl), and 1.8 (3H, d J 7Hz, CH_3).

2-(α-Bromoisobutyryl)aminobenzamide

Yield:88%, m.p. 179-180°C(lit.[17]191-192°C). ν_{max}: 3370, 3280, 3190, 1660, 1620, 1580, 1520, 1450, 1390, 1300, 725, and 700 cm^{-1}.

2-(α-Bromoisovaleroyl)aminobenzamide

Yield: 78 %, m.p. 124-127°C. ν_{max} 3400, 3200, 2960, 1660, 1620, 1580, 1520, 1400, and 760 cm^{-1}. δ_H 12.1 (1 H, s, NH), 8.3(2 H, br d, ar+NH), 7.8 (2 H, br d, ar+ NH), 7.5 (1 H, m, ar), 7.1 (1 H, m , ar), 4.6 (1 H, t, CHBr), 1.9 (2 H, m, CH_2), 1.8 (1 H, m, $CH(CH_3)_2$), 0.91 (3 H, d, CH_3), and 0.87 (3 H, d, CH_3).

2-(α-Chlorophenacyl)aminobenzamide 14

Yield: 75%, m.p. 156-158 °C. ν_{max} 3380, 3290, 3200, 1665, 1510, and 1300 cm^{-1}. δ_H 12.6 (1 H, s, NH), 8.4 (1 H, d, ar), 8.3 (1 H, br s, NH), 7.8 (2 H,b r d, ar+NH), 7.5- 7.3 (6 H, m, ar), 7.2 (1 H, m, ar), and 5.9 (1 H, s, CH).

2-(Phenylglyoxylyl)aminobenzamide

From 2-aminobenzamide and phenylglyoxylyl chloride[33]. Yield: 92%, m.p. 202-204 °C. δ_H 12.9 (1 H, s, NH), 8.8 (1 H, dd, ar), 8.2 (1 H, s, NH), 8.0-7.8 (3 H, m, ar), 7.6-7.4 (4 H, m, ar), 7.3 (1 H, s, NH), and 7.1 (1 H, m, ar). ν_{max} 3270, 3180, 1745, 1650-1580, 1500 and 890 cm^{-1}.

2-Hydroxymethyl-4(3H)-quinazolinone 17

2-Acetoxyacetylaminobenzamide (2.36 g, 10 mmol) was dissolved in aqueous potassium hydroxide (2 M, 15 ml) at ambient temperature, whereupon the solution obtained was heated (80°C) for 1 h. The cooled solution, acidified with acetic acid, gave **17** (1.42 g, 81%), m.p. 215°C (dec.) (lit.[34] 236-237°C, lit.[35] 214 °C).

2-Acetoxymethyl-4(3H)-quinazolinone 26

2-Hydroxymethyl-4(3H)-quinazolinone **17** (1.76 g, 10 mmol) was refluxed in acetic anhydride (10 ml) for 1 h. The solution was concentrated and cooled. The crystals formed were collected and washed with cold methanol to give **26** (1.90 g, 87%), m.p. 196–197°C (lit.[34] m.p. 196-197°C).

2-(α-Hydroxyethyl)-4(3H)-quinazolinone 1 ((-)-(S)-enantiomer)

Method A

2-Acetoxypropionylaminobenzamide **9** ($[\alpha]_D$ -103.4) (2.5 g, 10 mmol) was dissolved in aqueous potassium carbonate (50 ml, pH 9) and stirred at ambient temperature for 3 days. The resulting solution (pH 7) was extracted three times with EtOAc (20 ml). The combined organic phases were dried ($MgSO_4$) and evaporated in vacuum to give a solid material (1.5 g, 75%), m.p.190-192 °C(EtOAc), ($[\alpha]_D$ -41 (c 2.5 in EtOH)) (lit.[1] m.p. 189-190°C, $[\alpha]_D$ -24).

Method B, reduction with baker's yeast

Fresh baker's yeast (10 g) and sucrose (15 g) were suspended in water (100ml), after 1h at 30°C carbon dioxide evolved. 2-Acetyl-4(3H)-quinazolinone **2** (0.89 g, 4.7 mmol) was added and the suspension was stirred for 1 day. After addition of a warm (40°C) solution of sucrose (10 g) in water (25 ml) the suspension was stirred another 6 days. The mixture was worked up by addition of celite (10 g) followed by filtration. The filtrate was saturated with sodium chloride and extracted with EtOAc. The extract was dried ($MgSO_4$) and evaporated and the residue crystallized from EtOAc to give chrysogine (200mg, 22%) ($[\alpha]_D$ -36).

2-(α-Hydroxyethyl)-4(3H)-quinazolinone 1 ((+)-(R)-enantiomer)

Diethyl azodicarboxylate (0.36 ml, 2.3 mmol) and benzoic acid (0.244 g, 2 mmol) were dissolved in THF (20 ml). A solution of triphenylphosphine (0.53 g, 2 mmol) and **1** ($[\alpha]_D$- 40, 0.38 g) in THF (20 ml) was added dropwise. The resulting solution was stirred 18 h at room temperature. Evaporation of the solvent gave a crude product mixture which was flash chromatographed (Silica-gel, 2% CH_3OH in CH_2Cl_2) to give 2-benzoyloxyethyl-4(3H)-quinazolinone (350 mg, 59%).

2-Benzoyloxyethyl-4(3H)-quinazolinone (200 mg, 0.7 mmol) was stirred in potassium hydroxide (2 M, 3 ml) and EtOH (5 ml) overnight. Neutralization (2 M HCl), extraction (EtOAc), and evaporation gave **1** (100 mg, 78 %) ($[\alpha]_D$ +37 (c 2.5 in EtOH)).

2-Acetyl-4(3H)-quinazolinone 2

Method A

DMSO (3.4 ml) in CH_2Cl_2 (10 ml) was added to a cold (-60°C) solution of oxalyl chloride (2ml) in CH_2Cl_2 (60 ml). The solution was stirred for 10 min at -60°C, **1** (3.8 g, 20 mmol) dissolved in CH_2Cl_2 (50 ml) and DMSO (10 ml) was added. The reaction mixture was stirred for 2h at -60°C, triethylamine (14 ml) was added and the temperature was allowed to rise to room temperature. The solid formed was collected to give 2-acetyl-4(3H)-quinazolinone **2** (1.1g, 29%), m.p. 200-201°C (CH_3CN) (lit.[1] 174–176°C, lit.[3] 202-205°C, lit.[4] 197-200°C). ν_{max} 3160, 3060, 1710-1630, and 1600 cm^{-1}. δ_H 12.2 (1 H, br s, NH),8.2 (1 H, m, ar), 7.9-7.4 (3 H, m, ar), and 2.7 (3 H, s, CH_3). δ_C 194.0 (s), 159.9 (s), 147.3 (s), 147.1 (s) 134.7 (d), 128.8 (d), 128.5 (d), 126.1 (d),123.6 (s), and 24.7 (q).

Method B

2-(α,α-Dichloropropionyl)aminobenzamide **19** (13.05 g, 50 mmol) was dissolved in a mixture of EtOH (20 ml) and sodium hydroxide (aq., 4%, 100 ml) at 70°C. After 1h at this temperature the solution was cooled and acidified with hydrochloric acid. The precipitate formed was collected, washed with

water and dried to give **2** (7.5 g, 79 %), m.p. 200-201°C(CH_3CN).

2-Benzoyl-4(3H)-quinazolinone and 3-phenyl-1,4(1 H)-benzodiazepin-2,5-dione 24.

2-(Phenylglyoxylyl)aminobenzamide (13.4 g, 50 mmol) was dissolved in a solution prepared from ethanol (100 ml), water (50 ml) and potassium hydroxide (8 g) at 60°C. After 1h at this temperature the solution was acidified with acetic acid and diluted with water. The solid formed was collected and chromatographed (CH_2Cl_2/CH_3OH, 99.5/0.5) to give 2-benzoyl-4(3H)-quinazolinone (5.6g, 45%), m.p. 181-182 °C (lit.[36] 184°C). ν_{max} 3440, 3062, 2920, 1704, 1680, 1590, 925, and 780 cm^{-1}. m/z 250 (M^+), 105, and 77. δ_H 10.5 (1 H, s, NH), 8.5 (2 H, dd, ar), 8.4 (1 H, dd, ar), and 8.0-7.5 (6 H, m, ar) ppm. δ_C 185.6 (s), 161.0 (s), 147.6 (s), 146.0 (s), 134.8 (d), 134.3 (s), 134.0 (s), 131.8 (d), 129.4 (d), 129.4 (d), 128.4 (d), 126.9 (d), and 123.3 (s) ppm.

Further elution gave 3-phenyl-1,4(1 H)-benzodiazepin-2,5-dione (**24**) (2.9g, 23%), m.p. 220-222 °C. ν_{max} 3440, 3195, 3140, 1670, 1603, 1480, 770, and 695 cm^{-1}. m/z 250 (M^+), 222,119(base peak), and 77. δ_H 11.6 (1 H, br s, NH), 8.33 (1 H, dd, ar), 8.27 (2 H, m, ar), 7.8 (2 H, m, ar), and 7.6-7.5 (4 H, m, ar) ppm. δ_C 163.9 (s), 151.7 (s), 149.6 (s), 134.8 (d), 132.9 (s), 131.6 (d), 129.0 (d), 128.0 (d), 127.4 (d), 126.8 (d), 126.4 (d), and 120.9 (s) ppm.

2-(α-Ethoxybenzyl)-4(3H)-quinazolinone 16

2-(α-Chlorophenacyl)aminobenzamide **14** (2.88 g, 10 mmol) was dissolved in a mixture of ethanol, water and sodium carbonate. The solution was refluxed for 2h, and was then poured into cold water. The white solid which precipitated was collected and washed with water to give **16** (1.9 g, 68%), m.p. 141-142°C. ν_{max} 3360, 2940, 1680, 1605, 1470, 1340, and 1090 cm^{-1}. δ_H 9.7 (1 H, s, NH), 8.2 (1 H, dd, ar), 7.8-7.2 (8 H, m,, ar), 5.3 (1 H, s, CH), 3.7 (2 H, dq, diastereotopic CH_2), and 1.3 (3 H, t, CH_3). m/z 280 (M^+).

2-(α-Acetoxybenzyl)-4(3H)-quinazolinone 27

A solution of 2-aminobenzamide (1.36 g, 10 mmol) and *O*-acetylmandelic anhydride (3.7 g, 10 mmol) in dioxane (50 ml) was stirred over night at room temperature. A white solid precipitated and was collected to give **27** (1.69 g, 57%), m.p. 177 °C (EtOH) (lit.[16] 173 °C). $[\alpha]_D$ +67 (c 1 in EtOH). ν_{max} 3420, 3380, 3210, 1740, 1660, 1620, 1580, 1520, and 1220 cm^{-1} . δ_H 12.6 (1 H, br, NH), 8.5 (1 H, dd, ar), 8.1 (1 H, br, NH), 7.8 (1 H, dd, ar), 7.5-7.3 (7 H, m, ar), 7.1 (1 H, m, ar), 6.0 (1 H, s, CH), and 2.3 (3 H, s, CH_3). The mother liquor was treated with aqueous $NaHCO_3$ (10 %) and extracted with EtOAc. The organic phase was separated, dried ($MgSO_4$) and evaporated in vacuum to give a second crop (1.15 g, 40%) of 2-(α-acetoxybenzyl)-4(3H)-quinazolinone **27**. Total yield 97 %.

2-(α-Hydroxybenzyl)-4(3H)-quinazolinone 15

Method A

2-(α-Acetoxybenzoyl)aminobenzamide **27** (0.64 g, 2 mmol) was heated at 90 °C for 2h in aqueous Na_2CO_3 (10%). When the reaction mixture was cooled to room temperature a white solid precipitated. Recrystallization from EtOAc/toluene gave 2-(α-hydroxybenzyl)-4(3H)-quinazolinone **15** (220 mg,

39%), m.p. 218 °C (lit.[16] 208 °C) ($[\alpha]_D$= +63 (c= 1 in EtOH)). ν_{max} 3200, 3040, 3000, 1680, and 1605 cm^{-1}. δ_H 9.2 (1 H,br, NH), 8.2 (1 H,dd, ar), 7.7-7.4 (8 H,m, ar) 5.6 (1 H,d, J=3.2 Hz, OH), and 4.0 (1 H, d, J = 3.2 Hz, CH). m/z 252(M^+), 235.

Method B

Reduction of 2-benzoyl-4(3H)-quinazolinone with sodium borohydride.Yield: 69 %.

Method C

2-(α-Chlorophenacyl)aminobenzamide (0.54 g, 1.9 mmol) was dissolved in aqueous potassium hydroxide (2M, 20 ml) and heated (steambath) for 2h. The reaction was neutralized (AcOH) and the precipitate was collected to give **15** (0.41 g, 86%).

2-(α-Aminoethyl)-4(3H)-quinazolinone 30

Sodium azide (0.34g, 5.4 mmol) dissolved in water (5 ml) was added to a solution of 2-(α-bromoethyl)-4(3H)-quinazolinone (1.26 g, 5 mmol) in isopropanol (25 ml), whereupon the mixture was refluxed for 12 h. After evaporation of the solvent water and EtOAc was added, and the organic phase was separated, dried ($MgSO_4$), and evaporated to give 2-(α-azidoethyl)-4(3H)-quinazolinone **28** (72 %), m.p. 156 °C. ν_{max} 3180, 3130, 3040, 2140, 2100, 1660, 1300, 965, and 790 cm^{-1}. δ_H 10.7 (1 H, s, NH), 8.3 (1 H, dd, ar), 7.8-7.7 (2 H, m, ar), 7.5 (1 H, m, ar), 4.7 (1 H, q, CH), and 1.8 (3 H, d, CH_3). Found: C, 54.9; H, 4.1; N; 31.9. $C_{10}H_9N_5$ requires C, 55.8; H, 4.2; N, 32.5%.

2-(1-Azidoethyl)-4(3H)-quinazolinone was hydrogenated in a Parr apparatus with ethanol as solvent and Pd/C as catalyst, yield 98%, m.p. 192-194 °C. ν_{max} 3370, 3170, 3125, 3020, 2990, 1680, 1605, 1475, and 780 cm^{-1}. δ_H 8.2 (1 H, dd, ar), 7.7-7.6 (2 H, m, ar), 7.5 (1 H, m, ar), 4.0 (1 H, q, CH), 1.5 (3 H, d, CH_3).Found: C, 62.9; H, 5.9; N, 21.3%. $C_{10}H_{11}N_3Ox$ 0.25H_2O requires C, 62.0; H, 6.0; N, 21.7%.

2-(*N*-Trifluoroacetyl-α-aminopropionyl)aminobenzamide 21

2-Aminobenzamide (1.36 g, 10 mmol) and 4-methyl-2-trifluoromethyl-5(2H)-oxazolone **20b**[28] (2 g, 12 mmol) were dissolved in dry dioxane (50 ml). The solution was heated under reflux for 18 h and then poured into ice. The white solid formed was collected and recrystallized to give **21** (2.0g, 70%), m.p. 185-187°C. ν_{max} 3410, 3260, 1710-1690, 1650, 1630, 1590, and 760 cm^{-1}. δ_H 12.14 (1 H,s, NH), 9.57 (1 H,br d, NH), 8.45 (1 H,d, ar), 8.01 (1 H,br s, NH), 7.73 (1 H,dd, ar), 7.32 (1 H, m, ar), 7.0 (1 H, m, ar), 4.38 (1 H, dq, CH), and 1.42 (3 H,d, CH_3).

2-(*N*-Trifluoroacetyl-α-aminoethyl)-4(3H)-quinazolinone 22

Method A

Cyclization of **21** was effected by heating for 5 min above its melting point. Yield 90%, m.p. 272-275 °C (dec.). ν_{max} 3240, 1710, 1680, 1610, 1180, 780 cm^{-1}. δ_H 12.4 (1 H, s, NH), 9,9 (1 H, d, J = 6.9 Hz, NH), 8.1 (1 H, dd, ar), 7.8 (1 H, m, ar), 7.6 (1 H, dd, ar), 7.5 (1 H, dd, ar), 4.8 (1 H, p, J = 7 Hz, $CHCH_3$), 1.51 (3 H, d, J = 7 Hz, CH_3).

Method B

2-(α-Aminoethyl)-4(3H)-quinazolinone(1mmol) was treated with TFAA (1mmol) in ether (5ml) the solution was neutralized with $NaHCO_3$ (aq., 10%) and the precipitate was collected to give **22**, which

was identical with the product from the cyclization of **21**.

2-(α-Bromoethyl)-4(3H)-quinazolinone 11

The ring closure of *N*–(α–bromopropionyl)aminobenzamide was effected by reflux in toluene with *p*-toluenesulphonic acid as catalyst.Yield: 92%, m.p. 224 °C(dec.). ν_{max} 3180, 3040, 2980, 1680, 1610, 1470, and 775 cm^{-1}. δ_H 12.5 (1 H, s, NH), 8.1 (1 H, d, ar), 7.8 (1 H, m, ar), 7.7 (1 H, d, ar), 7.5 (1 H, m, ar), 5.1 (1 H, q, CHBr), and 2.0 (3 H, d, CH_3). m/z 254, 252 (M^+).

2-(α-Bromoethyl)-4(3H)-quinazolinone 11 (optically active)

2-Aminobenzamide (1.36 g, 10 mmol) was dissolved in pyridine (1.5 ml) and CH_2Cl_2 (50ml) and (–)-(S)-α-bromopropionyl chloride (1.72 g, 10 mmol) was added dropwise. The reaction mixture was stirred for 24 h at room temperature and was then washed with water, dried ($MgSO_4$)and evaporated to give **13** (2.2 g, 79 %).($[\alpha]_D$+ 20 (c 1 in EtOH)). *N*–(α–Bromopropionyl)aminobenzamide **13** was treated with aqueous Na_2CO_3 (10%) at room temperature for 10h to give **11** (69 %) ($[\alpha]_D$-50 (c 0.5 in DMF)).

2-(α-Chloroethyl)-4(3H)-quinazolinone 12 (optically active)

The method given for **11** was used.

Yield: 95 %, m.p. 220 °C (dec.) ($[\alpha]_D$+ 22 (c 0.5 in DMF)). ν_{max} 3400, 1685, 1609,1470, and 774 cm^{-1}. δ_H 10.0 (1H, br, NH),8.3 (1H, dd, ar), 7.7 (2H, m, ar), 7.5 (1H, m, ar), 5.0 (1H, q, CHCl), and 1.9 (3H, d, CH_3).

2-(α-Hydroxyisopropyl)-4(3H)-quinazolinone 25

2-(α-Bromoisobuturyl)aminobenzamide (0.29g, 1mmol) was heated to a clear solution in 2M NaOH (25ml). The resulting solution was stirred at room temperature overnight, and was then neutralized. The precipitate was collected and recrystallized to give **25** (120mg, 60%), m.p. 150-51°C(EtOH) (lit.[17]147–148°C). ν_{max} 3400, 3200, 3000, 1680, 1605, and 1200 cm^{-1}. m/z 204 (M^+-1).

2-(α-Hydroxyisopentyl)-4(3H)-quinazolinone 29

Yield 65 %, m.p. 142-144°C. ν_{max} 3180, 2960, 1680, 1610, 1470, 900, and 780 cm^{-1}.

(+)-(S)-α-Methoxy-α-trifluoromethyl-phenylacetyl chloride

(+)-(R)-α-Methoxy-α–trifluoromethylphenylacetic acid (2.0g) and oxalyl chloride (1.4g) were dissolved in dry CH_2Cl_2 (5ml). When dimethylformamide (1 drop) was added the reaction started immediately as indicated by evolution of CO_2(g). The mixture was stirred overnight, the solvent was evaporated and the residue was distilled to give (+)-(S)-MTPA-Cl (90%) ($[\alpha]_D$ 18.4 (l=0.1, neat)) (lit.[12] $[\alpha]_D$ 90.7 (l=0.5, neat).

Preparation of (+)-MTPA esters of chrysogine, **10b** from **S-chrysogine** and **10a** from **R-chrysogine**.

2-Hydroxyethyl-4(3H)-quinazolinone **1** (50 mg) was dissolved in dry CH_2Cl_2 (5 ml), pyridine (23mg) was added and finally (+)-(S)-MTPA-Cl (86 mg). The reaction was stirred at ambient temperature overnight and was then heated for 1 h. to about 50 °C. A white precipitate was filtered off (py.HCl) and the filtrate was washed with $NaHCO_3$ (10%, aq.) and finally water. The CH_2Cl_2 phase

was dried ($MgSO_4$) and evaporated in vacuum. The residue was flashchromatographed on a Silica-gel column (EtOAc:ligroin; 6:4).

NMR of MTPA esters of chrysogine

10a δ_H 11.0 (1 H, s, NH), 8.2 (1 H, dd, ar), 7.8-7.3 (8 H, m, ar), 5.93 (1 H, q, CH), 3.58 (3 H, d, J 1.6 Hz, OCH_3), and 1.73 (3 H, d, CH_3).

10b δ_H 11.4 (1 H, s, NH), 8.2 (1 H, dd, ar), 7.8-7.3 (8 H, m, ar), 5.97 (1 H, q, CH), 3.61 (3 H, d, J 1.6 Hz, OCH_3), and 1.80 (3 H, d, CH_3).

2-Ethyl-1,2,3,4-tetrahydro-4-oxoquinazoline-2-carboxylic Acid 23e

2-Aminobenzamide (13.6g, 0.1mol) and α-ketobutyric acid (9.2 g, 0.1mol) was mixed and heated to 140 °C for 2 min. to give a melt which soon solidified. The solid melt was readily soluble in ethanol and gradual addition of water gave a white solid, which was recrystallized to give **23e** (13.5g, 64%), m.p. 262-265°C (H_2O/EtOH). ν_{max} 3270, 2970, 1709, 1608, 900, and 753 cm^{-1}. δ_C 174.6 (s), 163.8 (s), 147.3(s), 133.1 (d), 127.1 (d), 117.1 (d), 114.4 (d), 114.2 (s), 73.1 (s), 29.3 (t), and 7.3 (q).

The following compounds were similarly prepared:

2-Methyl-1,2,3,4-tetrahydro-4-oxoquinazoline-2-carboxylic Acid 23a

Yield: 40%, m.p. 280°C (dec.)..ν_{max} 3475, 3330,1800, 1675, 1610, 1585,1510, and 755 cm^{-1} The relatively low yield is due to co-formation of compounds **2** and **3**.

2-Methyl-2-carbometoxy-1,2,3,4-tetrahydro-4-oxo-quinazoline 23b

m.p. 221-222°C.ν_{max} 3280, 3200, 1750, 1650, 1610, and 970 cm^{-1}. δ_H 8.5 (1H, s, NH), 7.6 (1H, dd, ar), 7.4 (1H, s, NH), 7.2 (1H, m, ar), 6.8 (1H, dd, ar), 6.7 (1H, m, ar), 3.6 (3H, s, OCH_3), and 1.6 (3H, s, CH_3) ppm. δ_C 173.8 (s), 163.4 (s), 146.7 (s), 133.4 (d), 127.3 (d), 117.6 (d), 114.3 (d), 69.9 (s), 52.6 (q), and 24.5 (q) ppm.

2-Benzyl-1,2,3,4-tetrahydro-4-oxoquinazoline-2-carboxylic Acid 23d

Yield: 72%, m.p. 206-208°C (lit.[21] m.p. 182-184°C). ν_{max} 3340, 3240, 3040, 1720, 1650-1610, 1250, and 760 cm^{-1}. δ_C 174.3 (s), 163.6 (s), 146.9 (s), 134.9 (s), 133.2 (d), 131.3 (d), 128.2 (d), 127.5 (d), 126.6 (d), 117.0 (d), 114.1 (d),113.4 (s), 73.3 (s), and 40.9 (t) ppm.

2-Bromomethyl-4(3H)-quinazolinone 18

Method A

A stirred mixture of 2-methyl-4(3H)-quinazolinone (32.0g, 0.2mol) and dry DMF (150ml) was treated with NBS (35.6g, 0.2mol) at 40°C. A clear solution was soon obtained which was left for 24h, whereupon the product formed was collected, washed with dry ether and dried to give 2-bromomethyl-4(3H)-quinazolinone (42.5g, 88%), m.p. >300°C (lit.[37]m.p.>300°C). ν_{max} 3030, 2880, 1680, 1609, 1470, and 775 cm^{-1}.

Method B

The cyclization method as described above for compound **11** was used. Yield: 90%.

Decarboxylation of 23e with diphenylphosphoryl azide

A solution of compound **23e** (2.2g, 10mmol), diphenylphosphoryl azide (2.4ml, 10mmol), and triethylamine (4ml) in DMA (25ml) was stirred for 24h, whereupon the reaction mixture was poured into water. The solid formed was collected and recrystallized to give 2-ethyl-4(3H)-quinazolinone (1.15g, 66%), m.p. 236-237°C (lit.[38]m.p. 235°C).

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