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Cyclic Guanidines. IX.[1] Synthesis of 2-Amino-3,4-dihydroquinazolines as Blood Platelet Aggregation Inhibitors[2]

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A series of aryl- or aralky-substituted 2-amino-3,4-dihydroquinazolines and related compounds were synthesized. The compounds were evaluated for inhibitory activity towards collagen- and ADP-induced aggregation of rat blood platelet *in vitro* and *ex vivo*. A group of 3-benzyl-substituted derivatives had potent activity. The structure-activity relationships are discussed.

Keywords——2-amino-3,4-dihydroquinazoline derivatives; 2-amino-3-substituted-benzyl-3,4-dihydroquinazoline; acylation of 2-amino-3,4-dihydroquinazoline; inhibition of platelet aggregation; structure-activity relationships

In the course of our studies on hypoglycemic tricyclic guanidines,[4] it has been found that 2-amino-4-phenyl-3,4-dihydroquinazoline (**20a**) shows potent blood platelet aggregation inhibitory action, whereas 2-amino-3,4-dihydroquinazoline (**17a**) has poor activity. Therefore it seemed of interest to examine the activity of 2-amino-3,4-dihydroquinazoline derivatives having various substituents. This paper deals with the synthesis and biological activity of various alkyl-, aryl- and aralkyl-substituted 2-amino-3,4-dihydroquinazolines and related compounds.

Reaction of 2-(N-benzylamino)benzylamine[5] (**1**) with cyanogen bromide gave 1-benzyl-2-imino-1,2,3,4-tetrahydroquinazoline (**2**). 2-Benzylamino-3,4-dihydroquinazoline (**4**) was obtained from 2-methylthio-3,4-dihydroquinazoline[6] (**3**) with benzylamine.

On heating 2-nitrobenzaldehyde (**5**), 2-nitrobenzyl chloride derivatives (**6**, **7**) and 2-aminobenzophenone (**8**), -acetophenone (**9**), and -propiophenone (**10**) with amines, such as aniline, benzylamine or phenethylamine, followed by reduction with sodium borohydride or by catalytic hydrogenation, 2-aminobenzylamine derivatives (**11**—**16**) were obtained. Treatment of **11**—**16** with cyanogen bromide afforded 3-, 4-, 5-, or 6-substituted 2-amino-3,4-dihydroquinazoline derivatives (**17**—**22**). In this procedure, the reaction of **9** or **10** with benzylamine did not give good results because of the formation of a by-product, a 4-substituted 2-(2-aminophenyl)quinoline derivative,[7] and the yields of **21c** and **22c** were poor. Accordingly, another method for the synthesis of **21c** was tried. Reaction of **9** with ethyl chloroformate gave 2-ethoxycarbonylaminoacetophenone (**23**). Heating **23** with benzylamine afforded 3-benzyl-4-methylene-3,4-dihydro-2(1H)-quinazolinone (**24**). In the nuclear magnetic resonance (NMR) spectrum of **24**, two distinct doublets were observed at δ 4.11 and 4.78 due to the exo-methylene hydrogens. Sodium borohydride reduction of **24** followed by chlorination and successive amination gave **21c** in a good yield.

Heating **11c** with formic acid gave 3-benzyl-3,4-dihydroquinazoline (**26**). 3-Benzyl-3,4-dihydro-2(1H)-quinazolinone[8] (**27c**) and -thione[9] (**28c**) were obtained by the reported method.

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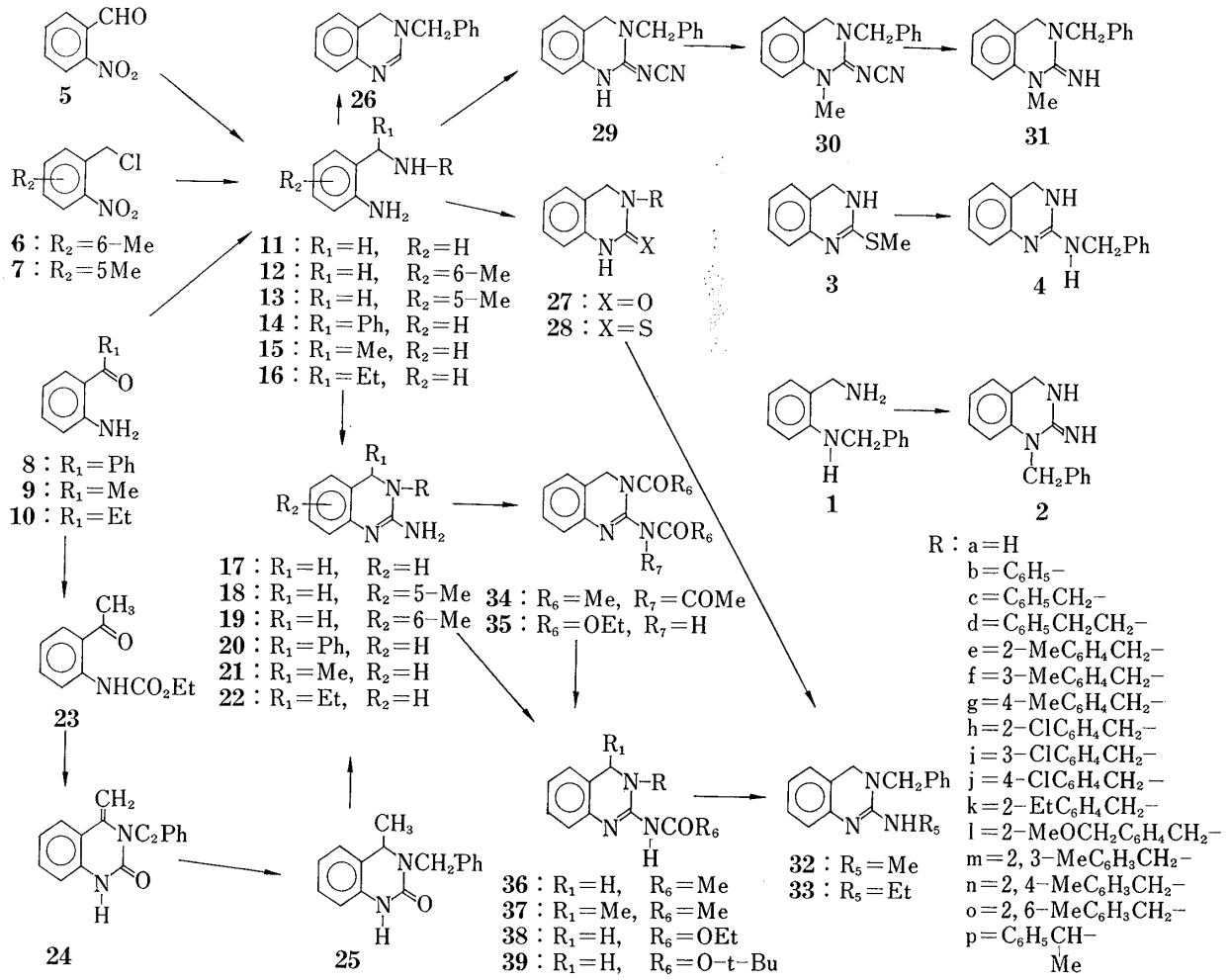

Chart 1

Heating **11c** with dimethyl cyanoimidodithiocarbonate at 180—200° gave the 2-cyanoimino derivative (**29**). Methylation of **29** with methyl iodide afforded the 1-methyl derivative (**30**), as in the similar methylation of 2-cyanoimino-1,2,3,4-tetrahydroquinazoline.[10] Refluxing **30** in *tert*-butyl alcohol (*tert*-BuOH) containing a small amount of hydrochloric acid yielded 3-benzyl-2-imino-1-methyl-1,2,3,4-tetrahydroquinazoline (**31**). Methylation of **28c** with methyl iodide, followed by amination with methyl- and ethylamine gave 3-benzyl-2-methylamino- and 3-benzyl-2-ethylamino-3,4-dihydroquinazoline (**32**, **33**), respectively.

Although the reaction of 2-amino-3,4-dihydroquinazoline (**17a**) with an equimolar amount of acetyl chloride gave many kinds of products, acetylation with a large excess of acetyl chloride afforded the tri-acetyl derivative (**34**) in good yield. Since the signals due to the two methyl groups were observed at the same chemical shift (δ 2.44) in the NMR spectrum, the structure of **34** is presumed to be 3-acetyl-2-(N,N-diacetylamino)-3,4-dihydroquinazoline; it was easily deacetylated on treatment with hot methanol or silica gel to give the 2-acetylamino derivative (**36a**).

After the reaction of 2-amino-3-benzyl-3,4-dihydroquinazoline derivatives (**17c**, **e**, **h**, and **21c**) with an excess of acetyl chloride, the crude reaction products were treated with silica gel

9) R.F. Smith, P.C. Breggs, R.A. Kent, J.A. Kent and E.J. Walsh, *J. Heterocycl. Chem.*, **2**, 157 (1965).
10) J.A. Bristol, *J. Heterocycl. Chem.*, **15**, 1409 (1978).

to give the 2-acetylamino derivatives (**36c**, **e**, **h**, and **37c**). Reduction of **36c** with lithium aluminum hydride gave the 2-ethylamino derivative (**33**), which was identical with a sample obtained from **28c**.

On the other hand, reaction of **17a** with an excess of ethyl chloroformate gave a mixture of the 2-N,3-diethoxycarbonyl derivative (**35**) and the 2-ethoxycarbonyl derivative (**38a**) which could be separated on recrystallization. Compound **38a** was identical with a sample obtained by catalytic reduction of 3-benzyl-2-ethoxycarbonylamino-3,4-dihydroquinazoline(**38c**) which was obtained by treatment of **17c** with ethyl chloroformate.

TABLE I. Aryl and Aralkyl Derivatives of 3,4-Dihydroquinazolines and Their Inhibition of Blood Platelet Aggregation

Compd.	Yield (%)	mp (°C)	IR (cm^{-1})	NMR[a] (δ)	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition of platelet aggregation[b] *in vitro* Coll[c] (μM)	ADP[d] (%)	*ex vivo*[e] Coll (%)
17a	66	214—216 (iso-PrOH)	1660 1570 1540	4.35	$C_8H_9N_3$	65.28 (65.47	6.16 6.20	28.55 28.67)	500		
20a	87	198—200 (iso-PrOH)	1620 1580 1530	5.50	$C_{14}H_{13}N_3$	75.31 (75.46	5.87 5.77	18.82 18.68)	20	35	15
2		132—134 (Me_2CO)	1650	5.33 4.59	$C_{15}H_{15}N_3$	75.92 (75.66	6.37 6.31	17.71 17.68)	9	0	
4		195—197 (EtOH–Et_2O)	1680 1630 1590	4.60 4.50	$C_{15}H_{15}N_3 \cdot HCl$	65.81 (65.86	5.89 5.90	15.35 15.75)	500	11	
17b	57	175—178 (Me_2CO)	1635 1535	4.68	$C_{14}H_{13}N_3$	75.31 (75.55	5.87 5.92	18.82 18.97)	60	22	
17c	70	224—226 (MeOH–Et_2O)	1650 1630 1620	4.52 4.25	$C_{15}H_{15}N_3 \cdot HCl$	65.81 (65.82	5.89 5.89	15.35 15.53)	48	32	36
17d	84	177—179 (MeOH–Et_2O)	1660 1630 1565	4.31	$C_{16}H_{17}N_3 \cdot HCl$	66.78 (66.80	6.30 6.32	14.60 14.63)	2	61	14
26		84—86 (PhH–p-ether)	1605 1590 1575	4.35 4.22	$C_{15}H_{14}N_2$	81.05 (81.06	6.35 6.48	12.60 12.58)	50	10	
27		207—209 (MeOH)	1655 1600 1480	4.55 4.30	$C_{15}H_{14}N_2O$	75.61 (75.59	5.92 5.96	11.75 11.77)	200		
28		202—204 ($CHCl_3$)	1535 1495	5.26 4.40	$C_{15}H_{14}N_2S$	70.83 (70.82	5.55 5.52	11.02 10.94)	140		
31		254—256 (EtOH–Et_2O)	1655 1605 1535	4.62 4.08	$C_{16}H_{17}N_3 \cdot HCl$	66.78 (66.74	6.30 6.37	14.60 14.67)	64	27	
32		154—156 (Me_2CO)	1530 1480	4.40	$C_{16}H_{17}N_3$	76.46 (76.14	6.82 6.84	16.72 16.56)	36		
21c	65	232—235 (MeOH–Et_2O)	1645 1545	4.38 3.02	$C_{16}H_{17}N_3 \cdot HCl$	66.78 (66.33	6.30 6.28	14.60 14.67)	15	47	84

a) Chemical shift of methylene or methine hydrogen. Solvent: DMSO-d_6.
b) Measured by Born's method[11] in rat platelet-rich plasma.
c) EC_{50}.
d) %inhibition at 0.25 mM test compound.
e) %inhibition 2 hr after *p.o.* administration (100 mg/kg) in rats.

11) G.V.R. Born, *Nature*, **194**, 927 (1962).

Table II. 2-Amino-3-benzyl-3,4-dihydroquinazoline Derivatives and Their Inhibition of Blatelet Platelet Aggregation

Compd.	Yield (%)	mp (°C)	IR (cm^{-1})	NMR (δ)	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition of platelet aggregation *in vitro* Coll (μM)	ADP (%)	*ex vivo* Coll (%)
17e	76	225—227 (EtOH–Et_2O)	1660 1625 1560	4.87 4.67	$C_{16}H_{17}N_3 \cdot HCl$	66.78 (66.82	6.30 6.39	14.60 14.62)	2	100	87
17f	72	189—191 (EtOH–Et_2O)	1660 1635 1590	4.40	$C_{16}H_{17}N_3 \cdot HCl$	66.78 (66.89	6.30 6.36	14.60 15.05)	2	67	100
17g	77	255—260 (EtOH–Et_2O)	1650 1625 1555	4.43	$C_{16}H_{17}N_3 \cdot HCl$	66.78 (67.01	6.30 6.37	14.60 14.75)	20	56	53
17h	90	207—209 (MeOH–Et_2O)	1655 1620 1550	4.76 4.56	$C_{15}H_{14}ClN_3 \cdot HCl$	58.46 (58.58	4.91 5.06	13.63 13.48)	50	100	14
17i	87	178—180 (MeOH–Et_2O)	1660 1630 1565	4.53 4.25	$C_{15}H_{14}ClN_3 \cdot HCl$	58.46 (58.71	4.91 4.97	13.63 13.79)	36	−13	
17j	61	226—228 (MeOH–Et_2O)	1665 1625 1560	4.50 4.20	$C_{15}H_{14}ClN_3 \cdot HCl$	58.46 (58.41	4.91 5.04	13.63 13.90)	8	−24	
17k	70	232—233 (MeOH–Et_2O)	1665 1630 1560	4.56 4.52	$C_{17}H_{19}N_3 \cdot HCl$	67.75 (67.88	6.68 6.66	13.92 14.12)	16	97	
17l	93	171—173 (MeOH–Et_2O)	1655 1560	4.55 4.45 4.42	$C_{17}H_{19}N_3O \cdot HCl$	64.25 (64.42	6.34 6.38	13.22 13.19)	24	0	
17m	78	211—213 (MeOH–Et_2O)	1660 1630 1570	4.11 3.81	$C_{17}H_{19}N_3 \cdot HCl$	67.65 (67.76	6.68 6.64	13.92 13.94)	10	17	
17n	82	257—259 (MeOH–Et_2O)	1660 1560	4.42 4.18	$C_{17}H_{19}N_3 \cdot HCl$	67.65 (67.66	6.68 6.73	13.92 13.66)	50	100	
17o	77	277—279 (MeOH–Et_2O)	1660 1580 1550	4.57 3.97	$C_{17}H_{19}N_3 \cdot HCl$	67.65 (68.13	6.68 6.64	13.92 14.09)	3	56	
17p	75	199—201 (MeOH–Et_2O)	1650 1620 1550	5.14 4.34 4.02	$C_{16}H_{17}N_3 \cdot HCl$	66.78 (66.50	6.30 6.20	14.60 14.47)	16	97	
18c	79	217—219 (EtOH)	1650 1590 1545	4.54 4.23	$C_{16}H_{17}N_3$	76.46 (76.40	6.82 6.77	16.72 16.90)	50	11	
19c	80	201—203 (MeOH–Et_2O)	1650 1630 1555	4.82 4.69	$C_{16}H_{17}N_3 \cdot HCl$	66.78 (66.79	6.30 6.25	14.60 14.68)	40	44	
20c	48	258—260 (MeOH–Et_2O)	1640 1540	5.30 4.99 3.92	$C_{21}H_{19}N_3 \cdot HCl$	72.09 (72.03	5.76 5.79	12.01 12.18)	20	89	31
21e	68	234—236 (EtOH–Et_2O)	1655 1560	4.48 4.28	$C_{17}H_{19}N_3 \cdot HCl$	67.65 (67.74	6.68 6.70	13.92 13.98)	15	34	100
21h	74	232—234 (MeOH–Et_2O)	1640 1540	4.62 4.40	$C_{16}H_{16}ClN_3 \cdot HCl$	59.64 (59.91	5.32 5.34	13.04 13.38)	15	47	84
22c	83	160—162 (iso-PrOH–Et_2O)	1650 1615 1555	4.30 4.85 4.32	$C_{17}H_{19}N_3 \cdot HCl$	67.65 (67.23	6.68 6.67	13.92 13.94)	25	100	83

Table III. Acyl Derivatives of 2-Amino-3-benzyl-3,4-dihydroquinazoline and Their Inhibition of Blood Platelet Aggregation

Compd.	Yield (%)	mp (°C)	IR (cm^{-1})	NMR (δ)	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition of platelet aggregation *in vitro* Coll (μM)	ADP (%)	*ex vivo* Coll (%)
36c	79	90—92 (iso-Pr_2O)	1570 1520	4.84 4.32	$C_{17}H_{17}N_3O$	73.09 (73.35	6.14 6.12	15.04 15.10)	50	11	
36e	79	99—101 (PhH–p-ether)	1590 1525	4.95 4.33	$C_{18}H_{19}N_3O$	73.70 (73.58	6.53 6.47	14.32 14.39)	500	0	
36h	65	124—126 (PhH–p-ether)	1580 1520	5.01 4.41	$C_{17}H_{16}ClN_3O$	65.07 (65.10	5.14 5.19	13.39 13.57)	170	7	
37c	34	95—97 (MeOH–Et_2O)	1735 1620	4.49 5.68 4.22	$C_{18}H_{19}N_3 \cdot HCl \cdot 1/2H_2O$	63.80 (63.58	6.25 6.44	12.40 12.01)	150	15	
38c	74	130—140 (EtOH)	1750 1640 1580	4.83 4.29	$C_{18}H_{19}N_3O_2 \cdot HCl \cdot 1/2H_2O$	60.93 (61.37	5.97 5.91	11.84 12.01)	18	15	
38e	95	110—112 (PhH–p-ether)	1630 1600	4.92 4.30	$C_{19}H_{21}N_3O_2$	70.57 (70.67	6.55 6.63	12.99 12.85)	280	6	
38h	81	108—110 (PhH–p-ether)	1630 1590	5.03 4.40	$C_{18}H_{18}ClN_3O_2$	62.88 (63.00	5.28 5.24	12.22 12.25)	110	6	
39e	74	135—138 (PhH–p-ether)	1630 1595	4.92 4.29	$C_{21}H_{25}N_3O_2$	71.77 (72.07	7.17 7.33	11.92 11.87)	7	0	

The inhibitory effects on blood platelet aggregation are summarized in Table I—III. An aryl or aralkyl group on the 2-amino-3,4-dihydroquinazoline molecule appears to be essential for the activity, as shown in Table I. 3-Aralkyl analogs (**17c**, **d**, and **21c**) showed the most potent action. 1-Benzyl- (**2**) and 3-phenyl (**17b**) derivatives showed potent inhibitory effects on the aggregation induced by collagen but only moderate activity for adenosine diphosphate-induced aggregation.

The 2-N-benzyl derivative (**4**) showed low activity. The 2-unsubstituted- (**26**), 2-one (**27c**), and 2-thione (**28c**) derivatives of 3-benzyl-3,4-dihydroquinazoline had no significant activity.

In the 2-amino-3-benzyl-3,4-dihydroquinazoline series, alkyl or phenyl substituents in the 1-, 2-N- and 4-positions and on the ring hardly affected the potency of the activity. On the other hand, substituents on the benzene ring of the 3-benzyl group appeared to increase the potency. In particular, the methyl substituted derivatives (**17e—g**, **21e**) have potent activity in both *in vitro* and *ex vivo*.

Generally, the potent active compounds obtained here showed relatively high acute toxicities in rats. In order to decrease the toxicity, 2-acylamino derivatives were prepared. However, these acyl compounds showed diminished effectiveness.

Experimental

All melting points are uncorrected. IR spectra were recorded with a Hitachi 285 spectrometer. MS spectra were determined on a JEOL OISG-2 MS spectrometer. NMR spectra were taken with a Hitachi Perkin-Elmer R-20B (60 MHz) or a Varian EM-360 (60 MHz) spectrometer with tetramethylsilane as an internal standard (δ value). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. For column chromatography, silica gel (Merck, 0.05—0.2 mm) was used. The usual work-up was as follows. The reaction mixture was concentrated to dryness *in vacuo*. The residue

was treated with H_2O or dil. NaOH solution and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated *in vacuo* to give the desired compounds, which were purified by recrystallization or silica gel chromatography, *etc.*

1-Benzyl-2-imino-1,2,3,4-tetrahydroquinazoline (2)——Compounds **1** obtained from 7.04 g (31 mmol) of 2-benzylaminobenzamide by Armergo's method[5] was dissolved in 300 ml of EtOH, and 3.07 g (20 mol) of BrCN was added to the mixture. After stirring at room temperature for 1 hr, the mixture was refluxed for 5 hr and concentrated to dryness *in vacuo*. The residue was worked up in the usual way to give 4.90 g (70%) of **2**.

2-Benzylamino-3,4-dihydroquinazoline (4)——A mixture of 3.06 g (10 mmol) of **3**[6] and 1.07 g (10 mmol) of benzylamine was heated at 140—150° for 30 min. The cooled reaction mixture was worked up in the usual way to give 2.10 g (75%) of the hydrochloride of **4**.

N-Benzyl 2-Aminobenzylamine (11c)——A solution of 16.0 g (0.106 mol) of 2-nitrobenzaldehyde and 11.3 g (0.106 mol) of benzylamine in 200 ml of benzene was refluxed for 5 hr, removing water with a Dean-Stark apparatus. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in 300 ml of EtOH. The solution was treated with 7.90 g (0.209 mol) of $NaBH_4$ in small portions and the mixture was stirred at room temperature overnight. The mixture was concentrated *in vacuo*. The residue was mixed with H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residue in 200 ml of EtOH was then catalytically hydrogenated with 0.30 g of PtO_2, and the catalyst was removed by filtration. The filtrate was evaporated down *in vacuo* to give **11c** as a crude pale brown oil in almost quantitative yield. The crude oil was used for subsequent reaction without further purification.

Other N-substituted 2-aminobenzylamines were prepared by the same method.

N-Benzyl 2-Amino-6-methylbenzylamine (12c)——A mixture of 4.20 g (23 mmol) of **6** and 10 g of benzylamine in 50 ml of EtOH was refluxed for 3 hr and worked up in the usual way to give a yellow oil. The oil in 50 ml of EtOH was hydrogenated with a platinum catalyst and worked up in the usual way to give 4.20 g (56%) of **12c** as an oil, which was used for subsequent reaction without further purification. Compound **13** was also prepared by the same method.

N-Benzyl 2-Aminobenzhydrylamine (14c)——Following a procedure similar to that used for the synthesis of **11c**, a mixture of 5.90 g (30 mmol) of 2-aminobenzophenone (**8**), 5.40 g (50 mmol) of benzylamine, and 0.1 g of *p*-toluenesulfonic acid was heated at 160° for 3 hr then treated with 2.0 g (50 mmol) of $NaBH_4$. The mixture was worked up in the usual way to give 5.0 g of a colorless oil, **14c**.

Other N-substituted α-methyl- or ethyl-2-aminobenzylamine (**15,16**) were prepared by the same method. These crude oils were used for subsequent reactions without further purification.

2-Amino-3-benzyl-3,4-dihydroquinazoline (17c)——A mixture of 8.30 g (39 mmol) of **11c** in 200 ml of EtOH was treated with 5.0 g (47 mmol) of BrCN and worked up in the usual way as described for the synthesis of **2** to give 6.50 g (70%) of **17c**.

Other 2-amino-3,4-dihydroquinazoline derivatives (**17**—**22**) shown in Table I and II were prepared by the same method.

2-Amino-3-benzyl-4-methyl-3,4-dihydroquinazoline (21c)——A mixture of 4.70 g (18.6 mmol) of **25** and 4.0 g (19 mmol) of PCl_5 in 100 ml of benzene was refluxed with stirring for 16 hr. The mixture was concentrated *in vacuo* and the residue was poured into ice-water. The mixture was neutralized with 10% K_2CO_3 solution under cooling and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The oily residue was dissolved in 50 ml of 5% NH_3–EtOH solution and the mixture was heated at 100—110° for 16 hr in a sealed tube. The mixture was concentrated *in vacuo* and the residue was triturated in Me_2CO to give 3.82 g (71%) of **21c**, which was identical with a sample from **15c**.

2-Ethoxycarbonylaminoacetophenone (23)——A solution of 4.05 g (30 mmol) of **9** in 50 ml of dry pyridine was treated with 4.9 g (45 mmol) of ethyl chloroformate with stirring at 10—15°. After stirring for 1 hr, the mixture was worked up in the usual way to give 5.10 g (82%) of **23**, mp 85—87° (benzene–petr. ether). IR ν_{max}^{KBr} cm^{-1}: 3200, 1710, 1640, 1590, 1520. NMR δ ($CDCl_3$): 6.85—8.6 (4H, m, aromatic protons), 4.20 (2H, q, CH_2), 2.60 (3H, s, CH_3), 1.29 (3H, t, CH_3). *Anal.* Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.58; H, 6.45; N, 6.72.

3-Benzyl-4-methylene-3,4-dihydro-2(1H)-quinazolinone (24)——A mixture of 2.07 g (10 mmol) of **23**, 1.30 g (12 mmol) of benzylamine, and 0.1 g of *p*-toluenesulfonic acid was heated at 150—160° for 1 hr. After cooling, the residue was treated with 10 ml of $CHCl_3$ to give 1.65 g (66%) of **24**, mp 211—213° ($CHCl_3$–petr. ether). IR ν_{max}^{KBr} cm^{-1}: 1660, 1595. NMR δ (DMSO-d_6): 7.26 (5H, s, Ph), 6.75—7.7 (4H, m, aromatic protons), 5.00 (2H, s, CH_2), 4.78, 4.11 (1H×2, d×d, J=2.5 Hz, =CH_2). *Anal.* Calcd for $C_{16}H_{14}N_2O$: C, 76.48; H, 5.64; N, 11.19. Found: C, 76.65; H, 5.67; N, 11.16.

3-Benzyl-4-methyl-3,4-dihydro-2(1H)-quinazolinone (25)——A mixture of 1.00 g (4.4 mmol) of **24** and 1.00 g (30 mmol) of $NaBH_4$ in 50 ml of EtOH was refluxed for 2 hr and worked up in the usual way to give 1.08 g (98%) of **25**, mp 139—141° (benzene–petr. ether). IR ν_{max}^{KBr} cm^{-1}: 1660, 1605. NMR δ ($CDCl_3$): 7.27 (5H, s, Ph), 6.65—7.1 (4H, m, aromatic protons), 4.74 (2H, d×d, CH_2), 4.38 (1H, q, CH), 1.30 (3H, d, CH_3). *Anal.* Calcd for $C_{16}H_{16}N_2O$: C, 76.17; H, 6.39; N, 11.10. Found: C, 76.36; H, 6.38; N, 10.98.

3-Benzyl-3,4-dihydroquinazoline (26)——A mixture of 6.00 g (28 mmol) of **11c** and 20 ml of 95% HCO_2H was refluxed for 10 hr and worked up in the usual way to give 5.60 g (89%) of **26**.

3-Benzyl-2-cyanoimino-1,2,3,4-tentrahydroquinazoline (29)——A mixture of 3.40 g (16 mmol) of **11c** and 2.50 g (17 mmol) of dimethyl cyanoimidodithiocarbonate was heated at 180—200° for 30 min. After cooling, the reaction mixture was treated with 30 ml of Me_2CO to give 2.40 g (57%) of **29**, mp 209—211° (Me_2-CO). IR ν_{max}^{KBr} cm^{-1}: 2170, 1625, 1600. NMR δ (DMSO-d_6): 7.32 (5H, s, Ph), 6.90—7.30 (4H, m, aromatic protons), 4.67 (2H, s, CH_2), 4.39 (2H, s, CH_2). *Anal.* Calcd for $C_{16}H_{14}N_4$: C, 73.26; H, 5.38; N, 21.36. Found: C, 72.97; H, 5.41; N, 21.19.

3-Benzyl-2-cyanoimino-1-methyl-1,2,3,4-tetrahydroquinazoline (30)——A solution of 4.70 g (19 mmol) of **29** in 100 ml of DMF was treated with 1.00 g (20 mmol) of NaH (50% oil suspension). After stirring at room temperature for 30 min, 3.00 g (20 mmol) of MeI was added to the mixture with stirring. The mixture was stirred for 16 hr and worked up in the usual way to give 3.85 g (77%) of **30**, mp 114—116° (benzene). IR ν_{max}^{KBr} cm^{-1}: 2155, 1650. NMR δ ($CDCl_3$): 7.39 (5H, s, Ph), 6.95—7.5 (4H, m, aromatic protons), 4.95 (2H, s, CH_2), 4.27 (2H, s, CH_2), 3.71 (3H, s, CH_3). *Anal.* Calcd for $C_{17}H_{16}N_4$: C, 73.89; H, 5.84; N, 20.28. Found: C, 73.62; H, 5.90; N, 20.02.

3-Benzyl-2-imino-1-methyl-1,2,3,4-tetrahydroquinazoline (31)——A mixture of 3.30 g (12 mmol) of **30** and 6 ml of conc. HCl in *tert*-BuOH was refluxed for 16 hr and worked up in the usual way to give 2.45 g (71%) of the hydrochloride of **31**.

3-Benzyl-2-methylamino-3,4-dihydroquinazoline (32)——A mixture of 2.54 g (10 mmol) of **28c** and 3.56 g (25 mmol) of MeI in 200 ml of MeOH was refluxed for 2 hr. The mixture was concentrated *in vacuo*. The residue was crystallized to give the 2-methylthio derivative of **28c** in quantitative yield. The crude intermediate was dissolved in a mixture of 10 ml of 40% $MeNH_2$ aqueous solution and 40 ml of EtOH, and the whole was refluxed for 5 hr. The mixture was made basic with 10% NaOH solution and concentrated *in vacuo*. The residue was mixed with H_2O and the crystals that separated were collected to give 2.42 g (93%) of **32**.

3-Benzyl-2-ethylamino-3,4-dihydroquinazoline (33)——a) Following a procedure similar to that used for the synthesis of **32**, a mixture of the 2-methylthio derivative obtained from 2.54 g (10 mmol) of **28c** and 10 ml of 70% $EtNH_2$ aqueous solution in 40 ml of EtOH was refluxed for 5 hr and worked up in the usual way to give 2.34 g (85%) of **33**, mp 107—109° (Me_2CO). IR ν_{max}^{KBr} cm^{-1}: 1520, 1470. NMR δ (DMSO-d_6): 7.31 (5H, s, Ph), 6.60—7.20 (4H, m, aromatic protons), 4.50 (2H, s, CH_2), 4.18 (2H, s, CH_2), 3.33 (2H, q, O-CH_2), 1.11 (3H, t, CH_3). *Anal.* Calcd for $C_{17}H_{19}N_3 \cdot 1/2H_2O$: C, 74.42; H, 7.35; N, 15.18. Found: C, 74.71; H, 7.10; N, 15.18.

b) $LiAlH_4$ (0.57 g) was added to a mixture of 2.80 g (10 mmol) of **36c** in 50 ml of dry Et_2O in small portions. The mixture was refluxed for 3 hr then poured into 100 ml of ice-water. The organic layer was separated and the water layer was extracted with Et_2O. The conbined Et_2O layer was worked up in the usual way to give 2.25 g (82%) of **33**, which was identical with a sample prepared from **28c**.

3-Acetyl-2-(N,N-diacetylamino)-3,4-dihydroquinazoline (34)——A mixture of 3.85 g (26.2 mmol) of **17a** and 16.6 g (105 mmol) of Et_3N in 50 ml of $CHCl_3$ was treated with 6.10 g (77.7 mmol) of AcCl in an ice-bath with stirring. After stirring at room temperature for 3 hr, the mixture was worked up in the usual way to give 4.90 g (69%) of **34**, mp 98—102° (benzene–petr. ether). IR ν_{max}^{KBr} cm^{-1}: 1720, 1700, 1675. NMR δ ($CDCl_3$): 7.30 (4H, m, aromatic protons), 4.82 (2H, s, CH_2), 2.44 (6H, s, CH_3), 2.28 (3H, s, CH_3). MS *m/e*: 273 (M^+), 231 (-$COCH_3$), 188 (-$COCH_3 \times 2$), 174, 146 (-$COCH_3 \times 3$). *Anal.* Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.33; N, 15.38. Found: C, 61.89; H, 5.56; N, 15.70.

2-Acetylamino-3,4-dihydroquinazoline (36a)——A solution of 1.60 g (6.9 mmol) of **34** in 30 ml of MeOH was refluxed for 30 min. The solution was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ and the solution was worked up in the usual way to give 0.88 g (67%) of **36a**, mp 166—168° (Me_2CO). IR ν_{max}^{KBr} cm^{-1}: 1630, 1590, 1490. NMR δ (DMSO-d_6): 7.00 (4H, m, aromatic protons), 4.50 (2H, s, CH_2), 1.96 (3H, s, CH_3). *Anal.* Calcd for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.37; H, 5.79; N, 21.45.

2-Acetylamino-3-benzyl-3,4-dihydroquinazoline (36c)——A mixture of 2.37 g (10 mmol) of **17c** and 3.0 g (30 mmol) of Et_3N in 50 ml of $CHCl_3$ was treated with 2.00 g (25 mmol) of AcCl and worked up as described for the synthesis of **34** to give 2.20 g (79%) of **36c**.

Other compounds **36e,h**, **37c**, **38c,e,h**, and **39c** were prepared by a similar method. The results are shown in Table III.

2-Ethoxycarbonylamino-3,4-dihydroquinazoline (38a)——a) Following a procedure similar to that used for the synthesis of **34**, a mixture of 1.35 g (9 mmol) of **17a** and 6 ml of Et_3N in 50 ml of $CHCl_3$ was treated with 2.50 g (23 mmol) of ethyl chloroformate to give a crude reaction mixture. This mixture was treated with 30 ml of Et_2O to give **38a** as an insoluble solid, 0.72 g (36%), mp 184—187° ($CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1650, 1610, 1530. NMR δ (DMSO-d_6): 7.00 (4H, m, aromatic protons), 4.50 (2H, s, CH_2), 4.00 (2H, q, O-CH_2), 1.18 (3H, t, CH_3). *Anal.* Calcd for $C_{11}H_{13}N_3O$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.52; H, 5.92; N, 19.10. The filtrate was concentrated *in vacuo* and the residue was recrystallized from benzene–petr. ether to give 0.69 g (26%) of **35a**, mp 120—122°. IR ν_{max}^{KBr} cm^{-1}: 1735, 1615, 1590. NMR δ ($CDCl_3$): 7.15 (4H, m, aromatic protons), 4.80 (2H, s, CH_2), 4.28, 4.19 (2H$\times$2, q, O-CH_2), 1.31, 1.27 (3H$\times$2, t, CH_3). *Anal.* Calcd for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42. Found: C, 58.04; H, 5.91; N, 14.70.

b) The hydrochloride of **38c** (1.50 g, 4.3 mmol) in 100 ml of MeOH was hydrogenated over 0.5 g of 10% Pd–C at room temperature under atmospheric pressure. After hydrogen absorption had ceased, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was worked up in the usual way to give 0.54 g (57%) of **38a**.

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