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Synthetic Studies on Quinazoline Derivatives. II. The Reactions of 2-Trichloro- and 2-Trifluoroacetamidobenzophenones with Primary Amines

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The reaction of 5-chloro-2-trichloroacetamidobenzophenone (**2a**) with several primary alkylamines in DMSO gave high yields of 3-substituted 6-chloro-3,4-dihydro-4-phenyl-4-trichloromethyl-2(1*H*)-quinazolinones **6**, which were found to be formed by base-catalyzed and/or thermal cyclization and simultaneous rearrangement of the isomeric 5-chloro-2-trichloroacetamidobenzophenone alkylimines **5**. Both compounds **5** and **6** were obtained when the reaction was effected in benzene. Treatment of the compound **2a** with bulky amines such as isopropylamine and cyclohexylamine gave, under similar conditions, the corresponding benzophenone imines **5d** and **5e** exclusively, and these could be transformed into the quinazolinones **6d** and **6e**, respectively, on heating in pyridine or HMPT. The reaction of N-substituted trichloroacetamidobenzophenones **2m** and **3n** with N-(2-aminoethyl)morpholine as well as ammonia in DMSO yielded the 1-alkylaminobenzophenone imines **4m—o**, which on treatment with trichloroacetyl chloride were readily cyclized to give the corresponding 1-substituted 4-trichloromethylquinazolinones **6m—o**. The trichloromethyl group of the 1-unsubstituted quinazolinones **6** was easily displaced by a nucleophile such as hydride, alkoxide or hydroxide under base catalysis to give the 3,4-dihydro-2(1*H*)-quinazolinone derivative **9**, **10** or **11** almost quantitatively, whereas the 1,3-disubstituted quinazolinone **6o** was not affected. The sodium borohydride reduction of the methylimine **5a** at room temperature mainly afforded the trichloroacetamidobenzhydrylamine **8a**, which underwent thermal cyclization to the quinazolinone **9a** *via* split of chloroform. In contrast, the reaction of 5-chloro-2-trifluoroacetamidobenzophenone (**2p**) with some primary alkylamines in DMSO produced the trifluoroacetamidobenzophenone alkylimines **5p—r**, which on treatment with sodium borohydride could be converted only to 3-substituted 6-chloro-3,4-dihydro-4-phenyl-2-trifluoromethylquinazolines **15**. These procedures were successfully utilized in syntheses of the imidazo[1,2-*c*]quinazolinone **16**, oxazolo[3,2-*c*]quinazolinones **17t** and **17v**, and 1,3-oxazino[3,2-*c*]quinazolinone **17u**.

Keywords——2-trihaloacetamidobenzophenone imines; 2-trihaloacetamidobenzhydrylamines; 3- and/or 4-substituted 3,4-dihydro-4-phenyl-2(1*H*)-quinazolinones; 1,3-migration of trichloromethyl group; base-catalyzed reaction; intramolecular cyclization; solvent effects; steric hindrance; reductive cleavage of carbon-carbon or carbon-oxygen bond by sodium borohydride; 3,4-dihydro-2-trifluoromethylquinazolines

Previously we reported[1] that 2-trichloro- and 2-tribromoacetamidophenyl ketones, on treatment with ammonia, were converted smoothly and in high yields to 4-substituted 2(1*H*)-quinazolinones *via* loss of the trihalomethyl function, whereas 2-trifluoroacetamidophenyl ketones yielded 4-substituted 2-trifluoromethylquinazolines by normal cyclodehydration. We wish to present here the results of our study on the reaction of 2-trichloro- and 2-trifluoroacetamidobenzophenones **2** with a variety of primary amines instead of ammonia.

Since we had found that the transformation of 5-chloro-2-trichloroacetamidobenzophenone (**2a**) to 6-chloro-4-phenyl-2(1*H*)-quinazolinone was best effected in dimethylsulfoxide (DMSO), we first treated the compound **2a** with *n*-propylamine in DMSO at room temperature (method D) to give slightly soluble light yellow crystals of the same empirical formula as the expected 5-chloro-2-trichloroacetamidobenzophenone *n*-propylimine (**5c**). The infrared (IR) spectrum of the product showed absorption bands at 3340—3050 cm^{-1} and a strong band at 1680 cm^{-1} indicating the presence of a different amide bond from the trichloroacetamide. The ^1H nuclear magnetic resonance (NMR) spectrum in DMSO exhibited a very characteristic multiplet

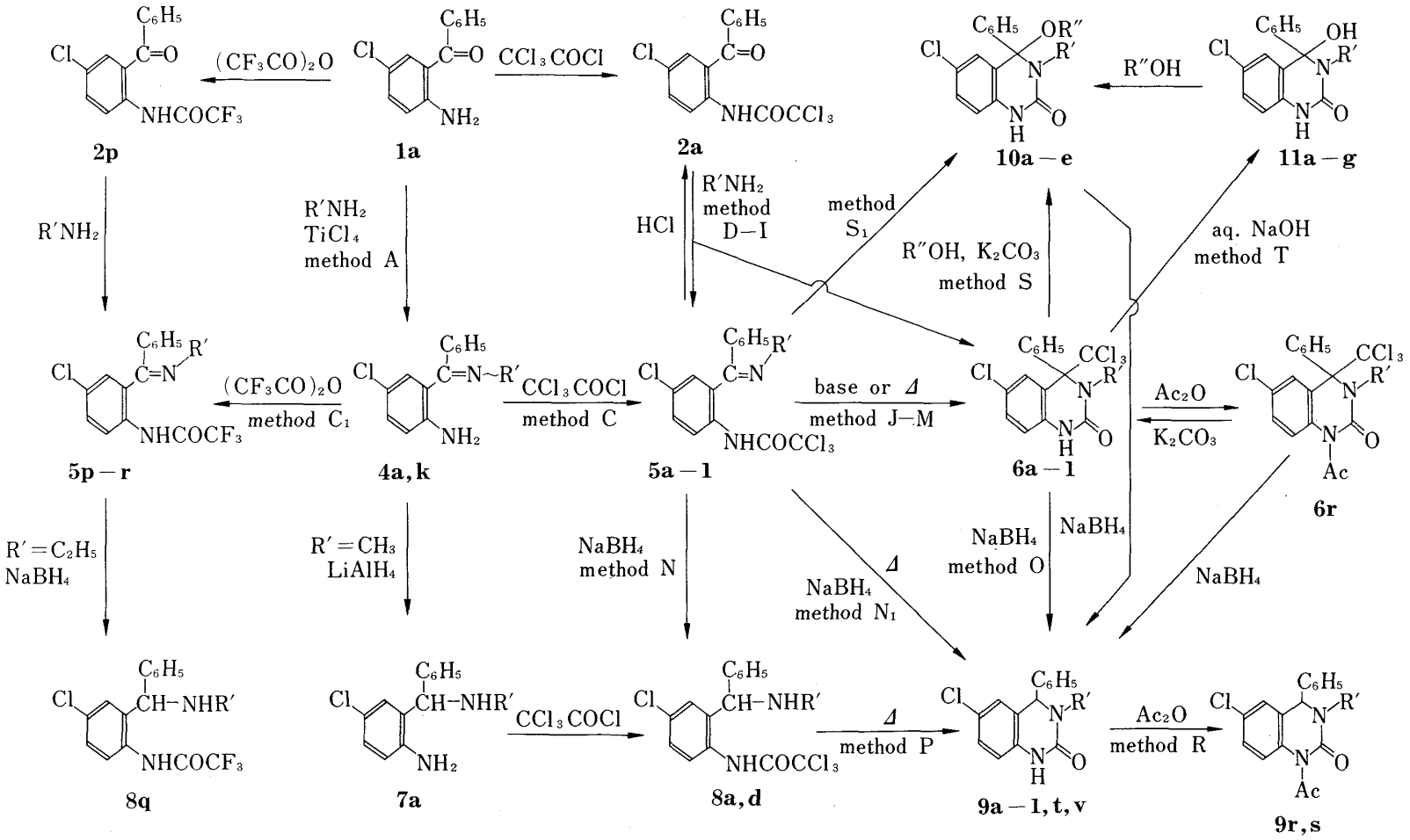
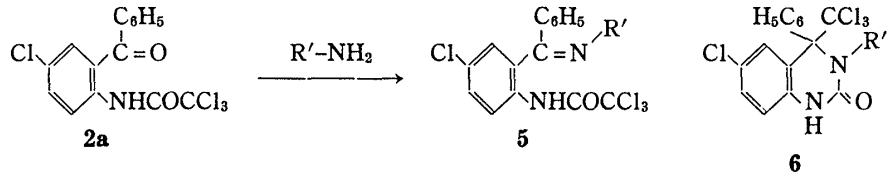


Chart 1

at δ 8.10—8.33 produced by one aromatic proton. The NH proton was observed at δ 9.97, a position compatible with that noted for 6-chloro-3,4-dihydro-4-ethoxy-4-phenyl-3-*n*-propyl-2(1*H*)-quinazolinone (**10c**) as listed in Table VIII. Moreover, the ultraviolet (UV) absorption spectrum was similar to those of the 3,4-dihydro-2(1*H*)-quinazolinones **9** and **10**. These data highly suggested that the product thus obtained was not the imine **5c** but 6-chloro-3,4-dihydro-4-phenyl-3-*n*-propyl-4-trichloromethyl-2(1*H*)-quinazolinone (**6c**). Reaction of **2a** with methylamine hydrochloride and ethylamine hydrochloride in the presence of triethylamine under similar conditions (method D_1) also yielded the analogous compounds **6a** and **6b** in high yields, respectively (Table I).

In order to confirm the structure **6** by spectral and chemical comparison, we attempted the preparation of the imines **5** *via* an alternative synthesis as shown in Chart 1. Thus, 2-aminobenzophenones **1** were reacted with an amine in the presence of titanium tetrachloride

TABLE I. Reaction of **2a** with Amines under Various Conditions



2a **5** **6**

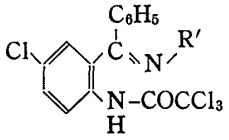
Compd.	R′	Solvent[a]	Reaction temp., °C	Reaction time, h	Method	Isolation[b]	Yield, % 5	Yield, % 6	Other products[c]
a	CH_3	DMSO	r.t.	20	D_1	a	0	88[d]	
		PhH	r.t.	4	G	b	28	33	
b	C_2H_5	DMSO	r.t.	24	D_1	a	0	74	
		PhH	r.t.	5	G	b	54	12	
c	*n*-C_3H_7	DMSO	r.t.	24	D	a	0	91	
		EtOH	60	3	E	c	57	13	a
		THF	Reflux	8	F	c	40	38	b
		HMPT	100	3	I	c	0	30	c
d	iso-C_3H_7	DMSO	r.t.	24	D_2	d	76	0	
		PhH	r.t.	4	G	d	84	0	
		HMPT	100	5	I	c	0	7	d
e	Cyclohexyl	DMSO	60	6	D_3	d	83	0	
		PhH	r.t.	4	G	d	91	0	
		HMPT	100	7	I	c	0	3	e
f	4-$CH_3C_6H_4$	PhH	60	5	G_1	d	67	0	
		HMPT	100	14	I_1	c	4	17[e]	
g	$CH_2C_6H_5$	DMSO	60	6	D_3	c	0	42	
		PhH	r.t.	3	G	d	84	0	
h	$(CH_2)_2N(C_2H_5)_2$	PhH	Reflux	5	H	c	56	21	
i	$(CH_2)_3N(CH_3)_2$	PhH	Reflux[f]	8	H	c	32	35	
j	$(CH_2)_2N$	EtOH	Reflux	7	E_1	d	0	72	
		PhH	Reflux[f]	5	H	b	48	16	
k	$(CH_2)_2N$ O	DMSO	r.t.	18	D	a	0	88	
		PhH	Reflux	8	H	b	72	6	
l	$(CH_2)_3N$ O	EtOH	Reflux	6	E_1	d	0	77	
		PhH	Reflux[f]	10	H	c	34	45	

a) DMSO, dimethyl sulfoxide; PhH, benzene; THF, tetrahydrofuran; HMPT, hexamethylphosphoric triamide.
b) a, crude; b, fractional crystallization; c, chromatography; d, recrystallization.
c) a, benzophenone **1a** (16%); b, quinazolinone **11c** (10%); c, **11c**, (58%); d, **1a** (5%), quinazolinone **11d** (35%), and isopropylurea **13d** (12%); e, **1a** (8%), 5-chloro-2-dichloroacetamidobenzophenone (5%) melting at 90—90.5°C [mp 89—90°C was reported in the literature: C. Podesva *et al.*, *Can. J. Chem.*, **46**, 435 (1968)], quinazolinone **11e** (28%), and 1-(2-benzoyl-4-chlorophenyl)-3-cyclohexylurea **13e** (31%) melting at 204—205 °C (lit.[4] mp 200—201°C).
d) This was shown by TLC to contain a small amount of **11a**.
e) In addition the starting material (46%) was recovered.
f) The reaction was carried out azeotropically with a water separator.

(method A) as described in the literature[2] to give a mixture of *syn* and *anti* forms of the benzophenone imines **4**. Separation of the isomers of the 2-morpholinoethylimine **4k** was accomplished by repeated fractional crystallization as described by Bell and co-workers.[3] Since an attempt to isolate the isomer of the methylimine **4a** failed, the mixture of the two isomers was, in turn, trichloroacetylated in benzene at room temperature (method C) to provide in 55% yield of the trichloroacetamidobenzophenone methylimine **5a**, which was isolated as a single material by recrystallization, along with the insoluble compound **6a** (15% yield). Analogously, *syn*-**4k** was trichloroacetylated to **5k**, and the *syn* and *anti* mixture of **4a** was trifluoroacetylated to **5p** (method C_1). The same imine **5r** was obtained by trifluoroacetylation of either isomer of the imine **4k**. The structure of these trihaloacetamidobenzophenone imines **5** was confirmed to be the *syn* form by comparison of their UV spectra with those of both forms of the benzophenone imines **4**.[3]

When the trichloroacetamidobenzophenone imine **5a** was treated with sodium bicarbonate in dimethylformamide (DMF) at room temperature (method J) or subjected to fusion at 150 °C (method K), it was readily transformed into the compound **6a**. In addition, the imine **5a** was easily hydrolyzed with hydrochloric acid to give the benzophenone **2a**, whereas the compound **6a** was quite stable under acidic conditions. These results show that the precursors of the compounds **6** are in fact the trichloroacetamidobenzophenone imines **5**.

TABLE II. 5-Chloro-2-trichloroacetamidobenzophenone Imines (**5**)



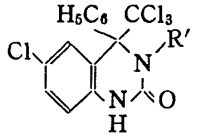
Compd.	R′	mp, °C	Recrystn. solvent	Formula	Analysis, % Calcd (Found) C	H	Cl	N
a	CH_3	131—132[a]	$CHCl_3$–EtOH	$C_{16}H_{12}Cl_4N_2O$	49.26 (49.25)	3.10 3.04	36.35 36.56	7.18 7.18)
b	C_2H_5	108—109	EtOH	$C_{17}H_{14}Cl_4N_2O$	50.53 (50.32)	3.49 3.52	35.09 35.23	6.93 6.87)
c	*n*-C_3H_7	86.5—87	EtOH	$C_{18}H_{16}Cl_4N_2O$	51.70 (51.64)	3.86 3.82	33.91 34.08	6.70 6.62)
d	iso-C_3H_7	173—173.5	$CHCl_3$–EtOH	$C_{18}H_{16}Cl_4N_2O$	51.70 (51.39)	3.86 3.74	33.91 33.86	6.70 6.70)
e	Cyclohexyl	183—184	$CHCl_3$–EtOH	$C_{21}H_{20}Cl_4N_2O$	55.05 (55.20)	4.40 4.28	30.95 30.78	6.11 6.13)
f	4-$CH_3C_6H_4$	184.5—185.5	$CHCl_3$–EtOH	$C_{22}H_{16}Cl_4N_2O$	56.68 (56.50)	3.46 3.42	30.42 30.43	6.01 6.03)
g	Benzyl	147.5—148	$CHCl_3$–EtOH	$C_{22}H_{16}Cl_4N_2O$	56.68 (56.78)	3.46 3.57	30.42 30.16	6.01 6.03)
h	$(CH_2)_2N(C_2H_5)_2$	86—87	iso-PrOH	$C_{21}H_{23}Cl_4N_3O$	53.07 (53.21)	4.88 5.07	29.84 30.08	8.84 8.86)
i	$(CH_2)_3N(CH_3)_2$	99—100	iso-PrOH	$C_{20}H_{21}Cl_4N_3O$	52.08 (52.24)	4.59 4.54	30.75 30.86	9.11 9.27)
j	$(CH_2)_2$N⟨ ⟩	136—137	$CHCl_3$–EtOH	$C_{22}H_{23}Cl_4N_3O_2$	54.23 (53.95)	4.76 4.72	29.10 28.98	8.62 8.66)
k	$(CH_2)_2$N⟨ O⟩	127.5—128.5	iso-PrOH	$C_{21}H_{21}Cl_4N_3O_2$	51.56 (51.46)	4.33 4.38	28.99 28.87	8.59 8.58)
l	$(CH_2)_3$N⟨ O⟩	116—117	iso-PrOH	$C_{22}H_{23}Cl_4N_3O_2$	52.51 (52.58)	4.61 4.62	28.18 27.96	8.35 8.32)

a) After melting, the compound soon solidified as the temperature was further raised. It finally decomposed at 250—251°C.

Since the imines **5a**—**c** could not be obtained by the reaction of **2a** with the corresponding amine in DMSO, we further examined the effects of several other solvents (Table I). When the compound **2a** was allowed to react with *n*-propylamine in ethanol at 60 °C, the imine **5c** was predominantly formed together with the compound **6c** and the deacylated benzophenone **1a** (method E). The analogous reaction with 2-piperidinoethylamine or 3-morpholinopropylamine in refluxing ethanol, however, afforded the compound **6j** or **6l** in good yield, respectively (method E_1). These reactions in tetrahydrofuran (method F) or benzene (method H) under reflux yielded both the imines **5** and the quinazolinones **6**. Similar results were obtained on treatment of **2a** with methylamine or ethylamine in benzene at room temperature in the presence of titanium tetrachloride (method G). These results suggest that the conversion of the imines **5** into the quinazolinones **6** is accelerated by a polar solvent.

In the case of bulky amines such as isopropylamine and cyclohexylamine, the present reaction, not only in benzene but also in DMSO, resulted in the exclusive formation of the imine **5d** or **5e** (Table I). However, when the compound **2a** was treated with 1.1 mol equiv of isopropylamine or cyclohexylamine in hexamethylphosphoric triamide (HMPT) at 100 °C (method I), the corresponding quinazolinone **6d** or **6e** was produced in very low yield, while the major products were the hydroxyquinazolinone **11d** or **11e** and the benzoylphenylurea **13d** or **13e** (Chart 2). Both **11** and **13** were easily obtained by alkali treatment of the quinazolinone **6d** or **6e** according to method T, which will be described later. The urea **13d** was identified by an unequivocal synthesis from the reaction of the aminobenzophenone **1a** with isopropyl isocyanate.[4] When the compound **2a** was made to react with 2—3 mol equiv of the amine

TABLE III. 6-Chloro-3,4-dihydro-4-phenyl-4-trichloromethyl-2(1*H*)-quinazolinones (**6**)



Compd.	R′	mp, °C(dec.)	Recrystn. solvent	Formula	Analysis, % Calcd (Found) C	H	Cl	N
a	CH_3	255	$CHCl_3$	$C_{16}H_{12}Cl_4N_2O$	49.26 (49.20	3.10 3.13	36.35 36.31	7.18 7.14)
b	C_2H_5	237—238	$CHCl_3$–EtOH	$C_{17}H_{14}Cl_4N_2O$	50.53 (50.79	3.49 3.60	35.09 35.03	6.93 7.05)
c	*n*-C_3H_7	238—239	DMF–iso-PrOH	$C_{18}H_{16}Cl_4N_2O$	51.70 (51.80	3.86 3.62	33.91 33.92	6.70 6.91)
d	iso-C_3H_7	249	$CHCl_3$–EtOH	$C_{18}H_{16}Cl_4N_2O$	51.70 (51.73	3.86 3.74	33.91 33.99	6.70 6.82)
e	Cyclohexyl	250	DMF–EtOAc	$C_{21}H_{20}Cl_4N_2O$	55.05 (55.02	4.40 4.80	30.95 30.75	6.11 5.94)
f	4-$CH_3C_6H_4$	234	DMF–$CHCl_3$	$C_{22}H_{16}Cl_4N_2O$	56.68 (56.28	3.46 3.39	30.42 30.84	6.01 6.36)
g	Benzyl	238	$CHCl_3$–EtOH	$C_{22}H_{16}Cl_4N_2O$	56.68 (56.72	3.46 3.23	30.42 30.21	6.01 6.19)
h	$(CH_2)_2N(C_2H_5)_2$	205.5—206	EtOH	$C_{21}H_{23}Cl_4N_3O$	53.07 (52.97	4.88 5.24	29.84 30.16	8.84 8.54)
i	$(CH_2)_3N(CH_3)_2$	203.5—204.5	DMF–$CHCl_3$	$C_{20}H_{21}Cl_4N_3O$	52.08 (52.11	4.59 4.44	30.75 31.07	9.11 9.05)
j	$(CH_2)_2$N⟨ ⟩	212—213	DMF–EtOAc	$C_{22}H_{23}Cl_4N_3O$	54.23 (53.92	4.76 4.83	29.10 28.91	8.62 8.55)
k	$(CH_2)_2$N⟨ O ⟩	226—227	DMF–$CHCl_3$	$C_{21}H_{21}Cl_4N_3O_2$	51.56 (51.78	4.33 4.30	28.99 29.10	8.59 8.60)
l	$(CH_2)_3$N⟨ O ⟩	223—224	$CHCl_3$–EtOH	$C_{22}H_{23}Cl_4N_3O_2$	52.51 (52.17	4.61 4.43	28.18 28.40	8.35 8.44)

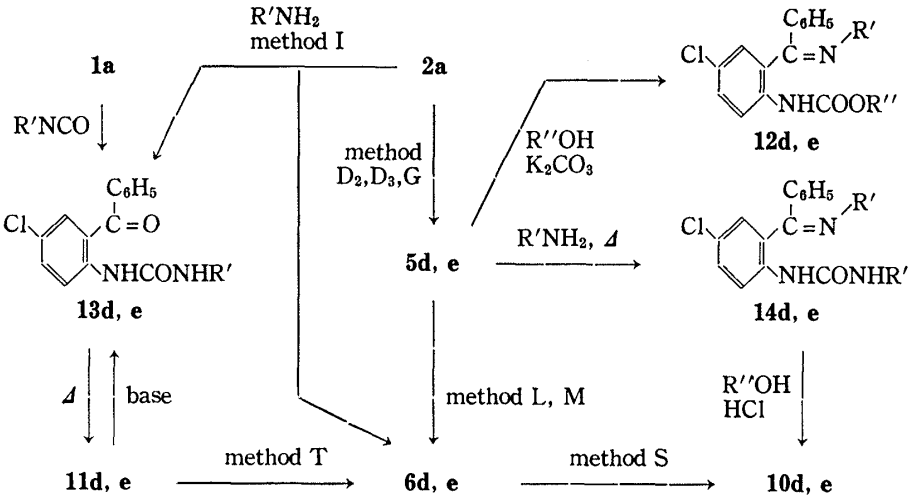
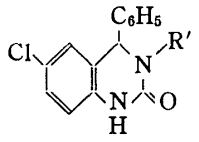
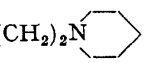
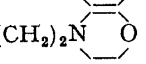
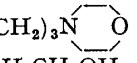


Chart 2

TABLE IV. 6-Chloro-3,4-dihydro-4-phenyl-2(1*H*)-quinazolinones (**9**) obtained from Compounds **6** by Method O

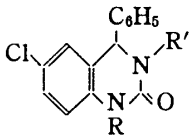


Compd.	R'	Yield,[a] %	mp, °C	Recrystn. solvent	Formula	Analysis, % Calcd (Found) C	H	Cl	N
a	CH_3	99	224—226[b]	EtOH	$C_{15}H_{13}ClN_2O$	66.06 (66.14	4.80 4.66	13.00 12.85	10.27 10.22)
b	C_2H_5	93	212.5—213.5	$CHCl_3$–EtOH	$C_{16}H_{15}ClN_2O$	67.02 (66.78	5.27 5.48	12.36 12.23	9.77 9.62)
c	n-C_3H_7	99	177—178	EtOH	$C_{17}H_{17}ClN_2O$	67.88 (68.02	5.70 5.71	11.79 11.95	9.31 9.31)
d	iso-C_3H_7	96	211.5—212.5	EtOH	$C_{17}H_{17}ClN_2O$	67.88 (67.50	5.70 5.67	11.79 12.10	9.31 9.22)
e	Cyclohexyl	98	225.5—226	EtOH	$C_{20}H_{21}ClN_2O$	70.48 (70.49	6.21 6.23	10.40 10.70	8.22 8.33)
f	4-$CH_3C_6H_4$	90	231.5—232.5	$CHCl_3$–EtOH	$C_{21}H_{17}ClN_2O$	72.31 (72.03	4.91 5.04	10.16 9.92	8.03 7.85)
g	Benzyl	93	151—152	EtOH–PB[c]	$C_{21}H_{17}ClN_2O$	72.31 (72.05	4.91 5.24	10.16 10.39	8.03 7.85)
h	$(CH_2)_2N(C_2H_5)_2$	98	182.5—183.5	EtOH	$C_{20}H_{24}ClN_3O$	67.12 (67.50	6.76 6.86	9.91 9.69	11.74 11.40)
i	$(CH_2)_3N(CH_3)_2$	99	176—177	EtOH	$C_{19}H_{22}ClN_3O$	66.37 (66.29	6.45 6.42	10.31 10.23	12.22 12.01)
j		94	199—200	$CHCl_3$–EtOH	$C_{21}H_{24}ClN_3O$	68.19 (68.11	6.54 6.60	9.58 9.79	11.36 11.27)
k		97	189—190	EtOH	$C_{20}H_{22}ClN_3O_2$	64.60 (64.60	5.96 5.85	9.53 9.38	11.30 11.19)
l		97	183—185	$CHCl_3$–EtOH	$C_{21}H_{24}ClN_3O_2$	65.36 (65.22	6.27 6.10	9.19 9.52	10.89 11.18)
t	CH_2CH_2OH	86	200—200.5	EtOH	$C_{16}H_{15}ClN_2O_2$	63.48 (63.55	4.99 4.81	11.71 11.57	9.25 9.23)
v	$CH_2CH(CH_3)OH$	89	203—206	EtOH	$C_{17}H_{17}ClN_2O_2$	64.46 (64.34	5.41 5.61	11.19 11.24	8.84 9.23)

a) Yields of crude, but sufficiently pure products.
b) Lit.[5] mp 224—226°C.
c) Petroleum benzin.

in DMSO at 100 °C, the benzimidoylphenylurea **14d** or **14e** was predominantly yielded *via* the corresponding imine **5d** or **5e**. This was verified by the following experiments: the reaction of **5d** with isopropylamine in DMSO at 100 °C afforded a good yield of the urea **14d**, whereas the reaction of the urea **13d** with or without isopropylamine by method I produced the quinazolinone **11d**. These results suggest that when R′ is a bulky radical the substitution of the trichloromethyl group of the imine **5** by the amine does occur predominantly over its transformation to the trichloromethylquinazolinone **6**. In fact, the imines **5d** or **5e** did not undergo transformation to the quinazolinone **6d** or **6e** on heating even in the presence of a base such as potassium carbonate or potassium hydroxide in an aprotic solvent such as DMF, DMSO or dioxane, whereas the imine **5c** could be slowly converted to **6c** by method J. This transformation was effectively accomplished by heating the imine **5d** or **5e** in a basic polar solvent such as pyridine (method L) or HMPT (method M); these procedures were suggested by the results obtained in method I.

TABLE V. 1,3-Disubstituted 6-Chloro-3,4-dihydro-4-phenyl-2(1*H*)-quinazolinones (**9**)



Compd.	R	R′	Method	Yield,[a] %	mp, °C	Recrystn. solvent[b]	Formula	Analysis, % Calcd (Found) C	H	Cl	N
o	CH_3	$(CH_2)_2N$ O	P	92[c]	178.5—179.5[d]	EtOH	$C_{21}H_{24}ClN_3O_2 \cdot C_4H_4O_4$	59.82 (59.77	5.62 5.54	7.06 7.07	8.37 8.50)
p	CH_3	C_2H_5	Q	93	142.5—144.5	EtOH	$C_{17}H_{17}ClN_2O$	67.88 (68.14	5.70 5.68	11.79 11.67	9.31 9.28)
q	CH_2-C$_6$H$_5$	C_2H_5	Q	86	90—91	EtOH–PB	$C_{20}H_{21}ClN_2O$	70.48 (70.23	6.21 6.45	10.40 10.55	8.22 7.85)
r	$COCH_3$	CH_3	R	50	128—129	EtOH	$C_{17}H_{15}ClN_2O_2$	64.87 (64.91	4.81 4.82	11.27 11.40	8.90 8.94)
s	$COCH_3$	$(CH_2)_2N(C_2H_5)_2$	R	75	87—87.5	IPE	$C_{22}H_{26}ClN_3O_2$	66.07 (65.78	6.55 6.68	8.86 8.83	10.50 10.49)

a) Yields after chromatography.
b) PB, petroleum benzin; IPE, isopropyl ether.
c) Yield based on benzhydrylamine **7o**.
d) Maleate.

We further examined the chemical properties of the trichloroacetamidobenzophenone imines **5** and trichloromethylquinazolinones **6**. Thus, the 1-unsubstituted derivatives **6** were found to be smoothly reduced with 2 mol equiv of sodium borohydride (SBH) in DMF at room temperature (method O) to give 3,4-dihydro-2(1*H*)-quinazolinones **9** in almost quantitative yields as listed in Table IV. Under the same conditions, treatment of the compound **5a** with SBH yielded the trichloroacetamidobenzhydrylamine **8a** as the major product together with the quinazolinone **9a** as a minor product, which was assumed to be formed *via* the trichloromethylquinazolinone **6**. The structure of **8a** was confirmed by an alternative synthesis from the lithium aluminum hydride (LAH) reduction of the benzophenone imine **4a**, followed by trichloroacetylation of the resulting diamine **7a**. When the compound **5a** was treated with 1 mol equiv of SBH in THF with ice-cooling, the compound **8a** was readily obtained (method N). When the same reaction was carried out under reflux for 1 h (method N_1), the quinazolinone **9a** was produced in good yield. The compound **6a** was also transformed to the quinazolinone **9a** under the same conditions (method O_1), although its reaction rate was considerably slower

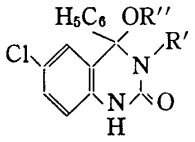
than that of the compound **5a**. Compound **8a**, in turn, could be converted to the quinazolinone **9a** in refluxing dioxane (method P). This cyclization was not effected in refluxing THF.

From these results it is suggested that the quinazolinone **9** would be produced by three separate pathways from the trichloroacetamidobenzophenone imine **5** (R=H, X=Cl), which can be derived from the trichloroacetamidobenzophenone **2** presumably *via* the cyclic carbinolamine **A** as shown in Chart 4. One pathway would comprise the formation of the trichloromethylquinazolinone **6** followed by nucleophilic substitution with a hydride ion *via* split of chloroform (methods O and O_1). This mechanism will be discussed in more detail later. Another pathway would be the ketimine reduction to the anion **D** and simultaneous ring-closure to the quinazoline intermediate **E** leading to the quinazolinone **9** *via* loss of chloroform (method N_1). The other pathway consist of protonation of the SBH reduction intermediate **D** to the benzhydrylamine **8** (method N) and its thermal cyclization to the intermediate **E** followed by loss of chloroform (method P).

In contrast, the isopropylimine **5d** was converted only to the benzhydrylamine **8d** in high yield by either method N_1 or O. Moreover, **8d** was not cyclized at all to the quinazolinone **9d** by refluxing in either dioxane or pyridine, presumably owing to the effect of steric hindrance.

The compound **6a** was then reacted with acetic anhydride under reflux to give the 1-acetyl derivative **6r**, which was readily deacylated to **6a** upon treatment with potassium carbonate in methanol. Treatment of **6r** with SBH by method O gave a quantitative yield of the compound **9a**, presumably *via* **6a**. The UV and IR spectra of **6r** were similar to those of the 1-acetylquinazolinone **9r**, which was prepared by the acetylation of **9a**.

TABLE VI. 4-Alkoxy-6-chloro-3,4-dihydro-4-phenyl-2(1*H*)-quinazolinones (**10**)

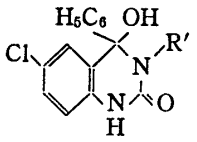


Compd.	R′	R″	Method	Yield,[a] %	mp, °C (dec.)	Recrystn. solvent[b]	Formula	Analysis, % Calcd (Found) C	H	Cl	N
a	CH_3	C_2H_5	S	100	279—280	EtOH–PB	$C_{17}H_{17}ClN_2O_2$	64.46	5.41	11.19	8.84
			S_1	98				(64.59	5.38	11.12	8.66)
b	C_2H_5	CH_3	S	100	193—195	$CHCl_3$–MeOH	$C_{17}H_{17}ClN_2O_2$	64.46	5.41	11.19	8.84
								(64.23	5.34	11.37	8.86)
c	*n*-C_3H_7	C_2H_5	S_1	95	207—209	$CHCl_3$–EtOH	$C_{19}H_{21}ClN_2O_2$	66.18	6.14	10.28	8.12
								(66.31	6.21	10.17	8.18)
d	iso-C_3H_7	C_2H_5	S	100	224—225	EtOH	$C_{19}H_{21}ClN_2O_2$	66.18	6.14	10.28	8.12
								(66.12	6.30	10.56	8.15)
e	Cyclohexyl	CH_3	S	97	161[c]	MeOH	$C_{21}H_{23}ClN_2O_2$	68.01	6.25	9.56	7.55
								(67.83	6.17	9.81	7.57)

a) Yields of crude products.
b) PB, petroleum benzin.
c) Melting point after sintering at 126 °C.

Treatment of the 1-unsubstituted derivatives **6** with potassium carbonate in an alcohol under reflux resulted in a clean conversion to the 4-alkoxy quinazolinones **10** (method S). The imines **5a** and **5c** were also converted to the corresponding quinazolinones **10a** and **10c** almost quantitatively under the same conditions (method S_1), presumably by way of the compounds **6a** and **6c**, respectively (Table VI). Treatment of the 1-unsubstituted quinazolinones **6** with aqueous sodium hydroxide in DMSO at room temperature (method T) gave the 4-hydroxyquinazolinones **11** (Table VII), which on treatment with alcohols were transformed into the

TABLE VII. 6-Chloro-3,4-dihydro-4-hydroxy-4-phenyl-2(1*H*)-quinazolinones (**11**) obtained by Method T



Compd.	R′	Yield,[a] %	mp, °C (dec.)	Recrystn. solvent[b]	Formula	Analysis, % Calcd (Found) C	H	Cl	N
a	CH_3	96	280—281[c]	$CHCl_3$–EtOH	$C_{15}H_{13}ClN_2O_2$	62.40 (62.02	4.54 4.62	12.28 12.73	9.70 9.60)
b	C_2H_5	92	177—179[d]	AcOEt	$C_{16}H_{15}ClN_2O_2$	63.48 (63.59	4.99 5.07	11.71 11.68	9.25 9.12)
c	*n*-C_3H_7	93	185—186	EtOH–PB	$C_{17}H_{17}ClN_2O_2$	64.46 (64.22	5.41 5.42	11.19 11.51	8.85 8.77)
d	iso-C_3H_7	79[e,f]	172—174	PhH–PB	$C_{17}H_{17}ClN_2O_2$	64.46 (64.30	5.41 5.38	11.19 11.35	8.85 8.79)
e	Cyclohexyl	64[e,g]	190—191	PhH–PB	$C_{20}H_{21}ClN_2O_2$	67.32 (67.37	5.93 5.86	9.93 10.00	7.85 8.04)
j	$(CH_2)_2N$	98	172—173[h]	PhH–PB	$C_{21}H_{24}ClN_3O_2$	65.36 (65.35	6.27 6.37	9.19 9.60	10.89 10.51)
k	$(CH_2)_2N$ O	88	158—160	Me_2CO	$C_{20}H_{22}ClN_3O_3 \cdot 1/2C_3H_6O$	61.94 (61.97	6.04 6.08	8.50 8.54	10.08 10.16)

a) Yields of crude products unless otherwise stated.
b) PB, petroleum benzin.
c) Lit.[5] mp > 200 °C.
d) Lit.[4] mp 172—173 °C.
e) Yields after chromatography.
f) In addition isopropylurea **13d** was isolated in 9% yield.
g) In addition cyclohexylurea **13e** was isolated in 31% yield.
h) Lit.[11] mp 202—203 °C.

alkoxyquinazolinones **10**. The compound **10a** was reduced more slowly by method O than the compound **6a** and thus heating was required to complete the reduction to **9a**. Metlesics and co-workers reported[5] that the compound **11a** on heating at 250 °C under a high vacuum was converted to 6-chloro-3-methyl-4-phenyl-2(3*H*)-quinazolinone. In contrast, on heating the compound **6a** under similar conditions with potassium carbonate, such a conversion did not occur. When R′=isopropyl or cyclohexyl, the reaction of the imine **5** by method S_1 resulted in the formation of the carbamate **12** as shown in Chart 2, owing to nucleophilic attack of the alkoxide ion on the trichloroacetamide carbonyl. Similar substitution has been observed in the case of the trichloroacetamidobenzophenones.[1] Incidentally, conversion of the compound **12d** to **10d** did not occur even under the conditions of method M.

On the other hand, we had also found[1] that the N-substituted trichloroacetamidobenzophenones **2m** and **2n** gave, on treatment with ammonia under conditions similar to those of method D, the benzophenone imines **4m** and **4n** (R′=H) together with 2(1*H*)-quinazolinones **3m** and **3n**, respectively, as shown in Chart 3. The analogous reaction of the benzophenone **2m** with 2-morpholinoethylamine gave 75% yield of the expected imine **4o** as a *syn* and *anti* mixture (method B), which was identical with that prepared from the aminobenzophenone **1m** by method A. When the imine **4m** or **4n** was allowed to react with trichloroacetyl chloride according to method C, the 3-unsubstituted 4-trichloromethylquinazolinone **6m** or **6n** was formed together with the 2(1*H*)-quinazolinone **3m** or **3n**. In this instance, the trichloroacetamidobenzophenone imines were never isolated. According to expectation, on treatment of the compounds **6m** and **6n** with a base such as sodium bicarbonate and potassium carbonate, the corresponding compounds **3m** and **3n** were readily accessible *via* loss of chloroform. This conversion did not take place in refluxing dioxane in the absence of a base.

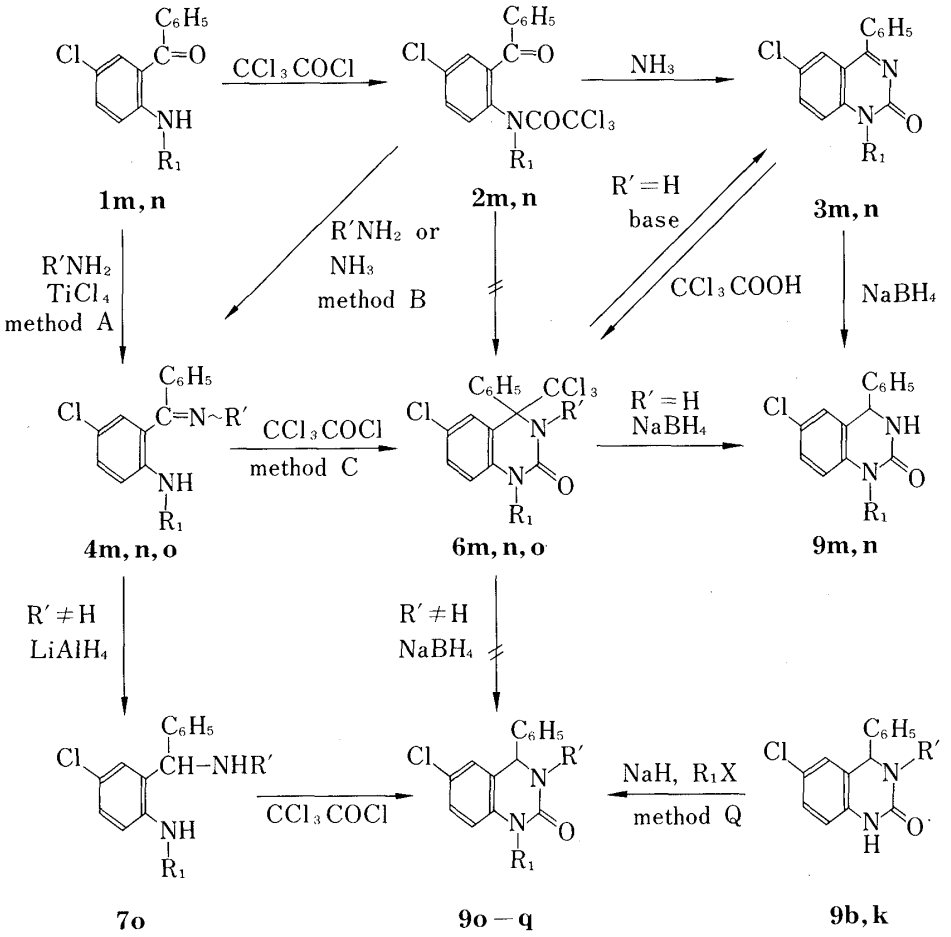


Chart 3

Reversely, the reaction of the compound **3n** with trichloroacetic acid in dioxane was found to give, *via* decarboxylation, a high yield of the compound **6n**. The same reaction in refluxing toluene, which had been used in the case of the 1-unsubstituted isoquinolines,[6] was effected in very low yield. The compounds **6m** and **6n** could be reduced with SBH quantitatively to the corresponding 3,4-dihydro-2(1*H*)-quinazolinones **9m** and **9n**, presumably by way of the compounds **3m** and **3n**. It has been reported[7] that reduction of the 2(1*H*)-quinazolinones **3** under similar conditions readily gives the dihydroquinazolinones **9**.

Trichloroacetylation of the morpholinoethylimine **4o** in refluxing benzene also resulted in cyclization to the 1,3-disubstituted 4-trichloromethylquinazolinone **6o** in high yield. In contrast with the 1-unsubstituted derivatives **6**, the compound **6o** was quite stable under such conditions as those of methods O, S, and T. Consequently, the 1,3-disubstituted quinazolinone **9o** was prepared by the following two alternative routes. The diamine **7o**, which was readily obtained by LAH reduction of the imine **4o**, was trichloroacetylated in benzene at room temperature to give a high yield of the cyclization compound **9o** *via* loss of chloroform. Treatment of the 1-unsubstituted quinazolinone **9k** with sodium hydride and methyl iodide gave the same product (method Q).

In view of the results described above, it is assumed that the formation of the 4-trichloromethylquinazolinone **6** from the imine **5** could arise *via* the cyclization intermediate cation B and simultaneous 1,3-migration of the trichloromethyl group as depicted in Chart 4. Its

TABLE VIII. Spectral Data for 2-Trihaloacetamidobenzophenone Imines and 3,4-Dihydro-2(1*H*)-quinazolinones

Compd.	UV λ_{max}^{EtOH} nm ($\varepsilon \times 10^{-3}$)	IR ν_{max}^{Nujol} cm^{-1}	NMR[a] δ ppm
5a	241(22.1), 271(9.6), 322(4.6)	1705(C=O), 1615(C=N)	3.23 (3H, s) 6.93 (1H, d, J=2.5 Hz), 7.03—7.60 (6H, m), 8.68 (1H, d, J=9 Hz), 15.1 (1H, s, NH)
5b	241(24.4), 272(10.4), 323(5.3)	1715(C=O), 1615(C=N)	1.23 (3H, t, J=7 Hz), 3.40 (2H, q, J=7 Hz), 6.90 (1H, d, J=2.5 Hz), 7.03—7.63, (6H m), 8.65 (1H, d, J=9 Hz), 15.3 (1H, s, NH)
5c	240(25.2), 273(10.9), 324(5.5)	1715(C=O), 1615(C=N)	0.87 (3H, t, J=7 Hz), 1.73 (2H, sextet, J=7 Hz), 3.33 (2H, t, J=7 Hz), 6.92 (1H, d, J=2.5 Hz), 7.05—7.60 (6H, m), 8.73 (1H, d, J=9 Hz), 15.4 (1H, s, NH)
5d	240(25.9), 274(11.2), 323(5.9)	1710(C=O), 1615(C=N)	1.20 (6H, d, J=6 Hz), 3.52 (1H, heptet, J=6 Hz), 6.85 (1H, d, J=2.5 Hz), 7.04—7.60 (6H, m), 8.70 (1H, d, J=9 Hz), 15.0 (1H, s, NH)
5k	241(25.6), 271(12.0), 324(5.6)	1705(C=O), 1620(C=N)	2.27—2.40 (4H, m), 2.68 (2H, t, J=7 Hz), 3.53 (2H, t, J=7 Hz), 3.57—3.73 (4H, m), 6.93 (1H, d, J=2.5 Hz), 7.10—7.60 (6H, m), 8.62 (1H, d, J=9 Hz), 15.2 (1H, s, NH)
5r	237(31.5), 267(12.5), 273(12.2), 322(4.7)	1710(C=O), 1617(C=N)	2.27—2.42 (4H, m), 2.68 (2H, t, J=7 Hz), 3.49 (2H, t, J=7 Hz), 3.57—3.73 (4H, m), 6.93 (1H, d, J=2.5 Hz), 7.07—7.63 (6H, m), 8.73 (1H, d, J=9 Hz), 15.2 (1H, s, NH)
6a	258(11.2), 307(2.1)	3350, 3200, 3080, 3050(NH), 1680(C=O)	2.77 (3H, s), 6.65 (1H, d, J=2 Hz), 6.98 (1H, d, J=8 Hz), 7.13—7.63 (5H, m), 8.1—8.4 (1H, m), 10.3 (1H, s, NH)
6b	259(12.7), 307(2.2)	3340, 3200, 3080, 3050(NH), 1680(C=O)	0.95 (3H, t, J=7 Hz), 2.83—3.30 (1H, m), 3.67—4.12 (1H, m), 6.76 (1H, d, J=2 Hz), 6.84 (1H, d, J=8 Hz), 7·08—7.55 (5H, m), 8.17—8.40 (1H, m), 9.77 (1H, s, NH)
6c	259(13.1), 307(2.1)	3340, 3200, 3080, 3050(NH), 1680(C=O)	0.42 (3H, t, J=7 Hz), 0.7—1.9 (2H, m), 2.4—3.1 (1H, m), 3.2—3.9 (1H, m), 6.57 (1H, d, J=2 Hz), 6.93 (1H, d, J=8 Hz), 7.1—7.7 (5H, m), 8.07—8.33 (1H, m), 9.97 (1H, s, NH)
6d	259(11.9), 310(2.3)	3340, 3200, 3080, 3060(NH), 1680(C=O)	1.08 (3H, d, J=6.5 Hz), 1.63 (3H, d, J=6.5 Hz), 3.45 (1H, heptet, J=6.5 Hz), 6.50 (1H, d, J=2 Hz), 6.87 (1H, d, J=8.5 Hz), 7.10—7.48 (5H, m), 8.11—8.35 (1H, m), 9.97 (1H, s, NH)
6m	260(13.6), 304(2.3)	3190, 3060(NH), 1670(C=O)	3.38 (3H, s), 6.04 (1H, s, NH), 6.89 (1H, d, J=9 Hz), 7.07 (1H, d, J=2 Hz), 7.23—7.46 (4H, m), 7.69—7.93 (2H, m)
6o	264(13.0), 307(2.2)	1660(C=O)	1.63—2.47 (6H, m), 2.5—3.3 (1H, m), 3.42 (3H, s), 3.4—3.6 (4H, m), 3.6—4.2 (1H,m), 6.83 (1H, d, J=2 Hz), 6.93 (1H, d, J=8 Hz), 7.16—7.53 (5H, m), 8.23—8.48 (1H, m)
6r	245(10.0)	1700(C=O)	2.63 (3H, s), 2.88 (3H, s), 6.77 (1H, d, J=2 Hz), 6.70—6.93 (1H, m), 7.27—7.47 (4H, m), 7.73 (1H, d, J=8.5 Hz), 8.17—8.37 (1H, m)
9b	260(10.1), 299(1.8)	3320, 3200, 3080, 3040(NH), 1670(C=O)	1.10 (3H, t, J=7 Hz), 2.63—3.23 (1H, m), 3.60—4.17 (1H, m), 5.53 (1H, s), 6.78 (1H, d, J=9 Hz), 6.93 (1H, d, J=2 Hz), 7.06 (1H, dd, $J_{7,8}$=9 Hz, $J_{5,7}$=2 Hz), 7.30 (5H, s), 9.25 (1H, s, NH)
9c	260(11.5), 299(2.1)	3320, 3200, 3080, 3040(NH), 1670(C=O)	0.88 (3H, t, J=7 Hz), 1.32—1.89 (2H, m), 2.57—3.05 (1H, m), 3.65—4.13 (1H, m), 5.47 (1H, s), 6.83 (1H, d, J=9 Hz), 7.08 (2H, dd, $J_{7,8}$=9 Hz, $J_{5,7}$=2 Hz), 7.37 (5H, s), 9.32 (1H, s, NH)
9m	260(12.0), 295(2.1)	3320, 3210, 3080 (NH), 1680(C=O)	3.27 (3H, s), 5.49 (1H, s), 6.88 (1H, d, J=8.5 Hz), 6.95 (1H, d, J=2 Hz), 7.12—7.40 (7H, m)[b]
9p	263(9.5), 296(2.0)	1650(C=O)	1.10 (3H, t, J=7 Hz), 2.70—3.30 (1H, m), 3.37 (3H, s), 3.60—4.20 (1H, m), 5.39 (1H, s), 6.80 (1H, d, J=8 Hz), 7.07 (1H, d, J=2 Hz), 7.17 (1H, dd, $J_{7,8}$=8 Hz, $J_{5,7}$=2 Hz), 7.28 (5H, s)
9r	243(10.9)	1710(C=O), 1690(C=O)	2.50 (3H, s), 3.23 (3H, s), 5.23 (1H, s), 7.06—7.43 (7H, m), 7.8 (1H, d, J=9 Hz)
10b	254(16.1), 299(1.9)	3340, 3200, 3080, 3050(NH), 1670(C=O)	0.97 (3H, t, J=7 Hz), 3.10 (3H, s), 3.30 (2H, q, J=7 Hz), 6.78 (1H, d, J=2 Hz), 6.87 (1H, d, J=9 Hz), 7.17 (1H, dd, $J_{7,8}$=9 Hz, $J_{5,7}$=2 Hz), 7.25—7.63 (5H, m), 10.07 (1H, s, NH)
10c	254(16.2), 300(1.9)	3300, 3180, 3080, 3040(NH), 1675(C=O)	0.67 (3H, t, J=7 Hz), 1.22 (3H, t, J=7 Hz), 1.0—1.9 (2H, m), 2.92—3.77 (4H, m), 6.75 (1H, d, J=2 Hz), 6.82 (1H, d, J=9 Hz), 7.10 (1H, dd, $J_{7,8}$= 9 Hz, $J_{5,7}$=2 Hz), 7.20—7.67 (5H, m), 9.93 (1H, s, NH)

a) The solvent was $CDCl_3$ except in the cases of **6a** and **6c** (DMSO-d_6) and **6d** and **9m** ($CDCl_3$–DMSO-d_6).
b) 1H was removed on addition of D_2O.

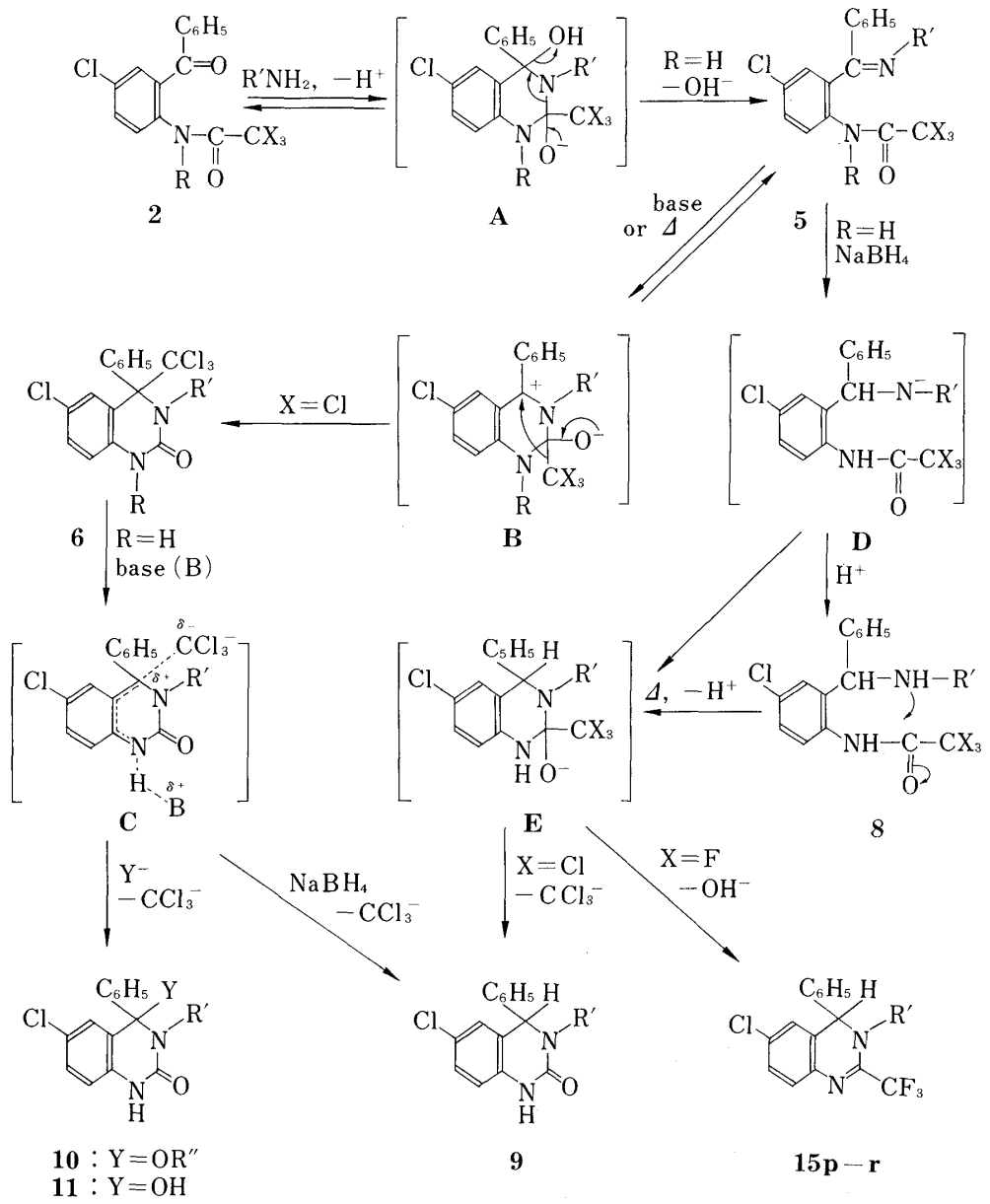


Chart 4

formation would be favored with the N-alkylated trichloroacetamide derivative **5**, but hindered by a bulky substituent R′ at the imino nitrogen. Although steric difference of the compound **5** (X=Cl) was indeed a major factor that influenced its conversion to the quinazolinone **6**, heating and base treatment with a polar solvent facilitated this isomerization. When R=H, displacement of the trichloromethyl group of the compound **6** presumably proceeds by base-catalyzed attack of a nucleophile *via* the transition state **C** for the S_N2 mechanism. This postulate is based on the observation that the 1-unsubstituted quinazolinones **6**, even if R′ was a bulky group, gave a high yield of the corresponding substitution product **9**, **10** or **11** on treatment with hydride, alkoxide or hydroxide anion, whereas the 1,3-disubstituted derivatives, *e.g.* **6o**, did not undergo these reactions.

The reaction of 5-chloro-2-trifluoroacetamidobenzophenone (**2p**) with some alkylamines was also investigated (Chart 1). When the compound **2p** was treated with N-(2-aminoethyl)-morpholine in DMSO under conditions similar to those of method D, the main product that was isolated was not the quinazoline-type compound, but the trifluoroacetamidobenzophenone

imine **5r**, which was identical with that prepared by trifluoroacetylation of the imine **4k**. Under similar conditions, the methylimine **5p** and the ethylimine **5q** were produced on treatment of the compound **2p** with the corresponding amine. In contrast with the trichloroacetamide derivative **5a**, the compound **5p** was recovered unchanged after treatment by methods J, K, and S_1.

Treatment of the compound **5p** with SBH by method O, however, afforded a good yield of 6-chloro-3,4-dihydro-3-methyl-4-phenyl-2-trifluoromethylquinazoline (**15p**), presumably *via* the intermediates **D** and **E**, followed by loss of a hydroxy ion as shown in Chart 4. Under the same conditions, the 2-trifluoromethylquinazoline **15r** ($R'=CH_2CH_2N\langle O \rangle$) was also produced in 87% yield from the imine **5r**. When the imine **5q** ($R'=C_2H_5$, X=F) was treated with SBH in THF with ice-cooling, the trifluoroacetamidobenzhydrylamine **8q** was isolated. The compound **8q** did not react in refluxing THF, but could be transformed into the quinazoline **15q** in refluxing dioxane, presumably *via* the intermediate **E**, whereas the trichloroacetamide derivative **8a** was cyclized to the quinazolinone **9a** under the same conditions. These results confirmed that the trifluoromethyl group very seldom underwent nucleophilic substitution involving carbon-carbon bond fission.[8] Facile elimination of a trichloromethyl anion from the trichloroacetyl group has been been attributed to the lower activation energy for decarboxylation of trichloroacetic acid than for that of trifluoroacetic acid.[9]

We have successfully extended this reaction to alkylenediamine and aminoalkanol (Chart 5). Thus, reaction of the compound **2a** with ethylenediamine in ethanol at room temperature readily afforded a high yield of the expected imidazo[1,2-*c*]quinazolinone **16**. This structure was confirmed by an alternative synthesis, *i.e.*, by reacting 2-methoxycarbonylamino-5-chlorobenzophenone with ethylenediamine in refluxing toluene.[10] Compound **2a** was then treated with monoethanolamine at 90 °C under conditions similar to those described in method D to give the oxazolo[3,2-*c*]quinazolinone **17t**, which was also identified by the synthesis from 2-ethoxycarbonylamino-5-chlorobenzophenone.[11] The same reaction according to method E_1 produced both the compound **17t** and the trichloromethylquinazolinone **6t** in a ratio of about 1:1. The latter compound was readily cyclized to the former in quantitative yield by heating it with ethanolic potassium hydroxide. Similarly, treatment of the compound **2a** with 1-amino-2-propanol in refluxing *n*-propanol yielded the oxazole derivative **17v** and the intermediate **6v** together with the deacylated compound **1a**. Thus, compound **2a** was reacted with 3-aminopropanol by method E_1, and then the reaction mixture was treated *in situ* with potassium hydroxide to give a high yield of the oxazinoquinazolinone **17u**.

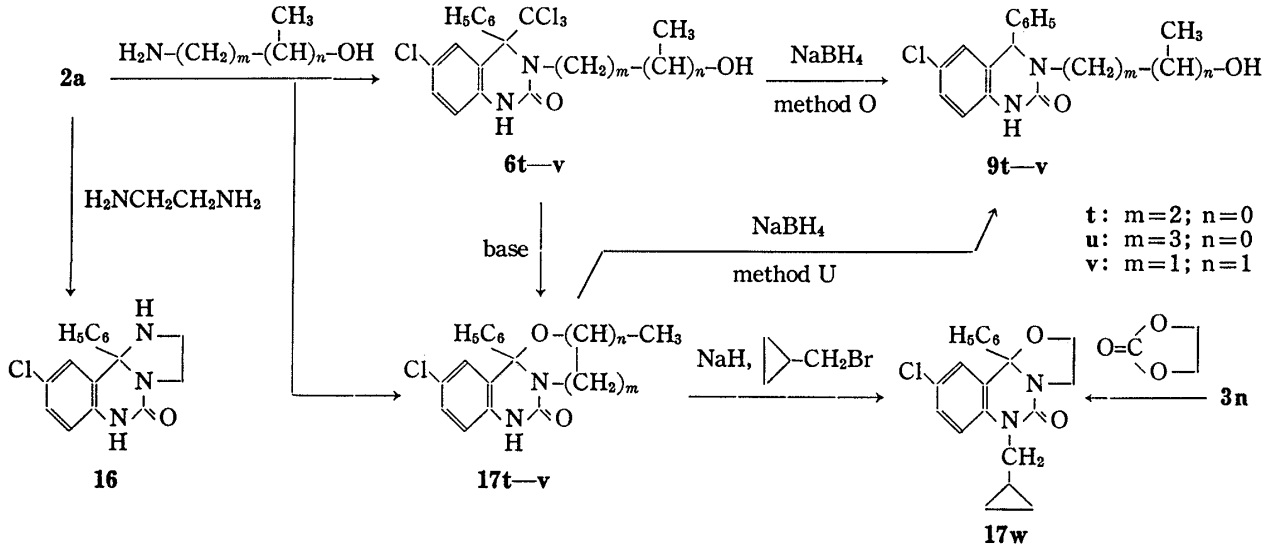


Chart 5

When the oxazole compound **17t** was treated with SBH in EtOH at room temperature, the 3,4-dihydro-3-(2-hydroxyethyl)-2(1*H*)-quinazolinone **9t** was obtained in quantitative yield (method U). This structural assignment was corroborated by the reduction of the compound **6t** by method O. Similarly, the oxazole derivative **17v** also underwent reductive cleavage of the oxazole ring to yield the compound **9v**. Under the same conditions, the reaction rate of the oxazine derivative **17u** to the compound **9u** was significantly slower than that of the oxazole compounds. Treatment of the compound **17t** with sodium hydride and cyclopropylmethyl bromide gave the oxazoloquinazolinone **17w**, which was conveniently prepared in good yield from the quinazolinone **3n** by the addition of ethylene carbonate to the azomethine bond. The N-substituted oxazoloquinazolinone **17w** did not undergo, on treatment according to method U, cleavage of the oxazole ring.

Experimental[12]

2-Amino-5-chlorobenzophenone Methylimine (4a)——This imine was prepared by the reaction of 2-amino-5-chlorobenzophenone (**1a**) with methylamine as described in method A below. The crude product was shown by TLC (benzene–AcOEt (5: 2) as a developer) to be mostly a mixture of *syn* and *anti* isomers. It was not isolated in crystalline form, but was used directly in further reactions. IR (neat): 3470, 3380, 3200 (NH_2), 1610 (C=N).

2-Amino-5-chlorobenzophenone 2-Morpholinoethylimine (4k)——Method A: A solution of 9.27 g (40 mmol) of **1a** and 52.0 g (400 mmol) of N-(2-aminoethyl)morpholine in 300 ml of dry benzene was treated with a solution of 4.6 g (24 mmol) of $TiCl_4$ in 40 ml of dry benzene overnight.[2] The crude product was crystallized from EtOH–*n*-hexane to give 10.5 g (76%) of **4k** as a mixture of two isomers, each of which was isolated by repeated fractional crystallization from EtOH. The *syn* isomer (total yield 37%) had the lower *Rf* spot on TLC ($CHCl_3$–MeOH (4: 1) as a developer) and melted at 139—140°C (lit.[3] mp 140—142°C), while the *anti* isomer (total yield 30%) had the higher *Rf* spot and melted at 106—108°C (lit.[3] mp 112—114°C).

5-Chloro-2-methylaminobenzophenone 2-Morpholinoethylimine (4o)——A. From **1m**: 5-Chloro-2-methylaminobenzophenone (**1m**) (4.91 g) was treated according to method A with 26 g of N-(2-aminoethyl)-morpholine and 2.28 g of $TiCl_4$. Repeated fractional crystallization of the crude product from EtOH gave 0.925 g of *syn*-**4o** as colorless prisms, mp 125.5—126°C (lit.[3] mp 123—125°C).

From the mother liquor of the first recrystallization, 0.45 g of *anti*-**4o** was isolated by repeated crystallization from EtOH as light yellow prisms, mp 101—101.5°C (lit.[3] mp 100—102°C).

From the above filtrates, 4.43 g of a mixture of the isomers melting at 90—91°C was obtained. The total yield of *syn*- and *anti*-**4o** based on **1m** was 81%.

B. Method B: To a solution of 1.96 g (5 mmol) of 5-chloro-2-(N-methyl-trichloroacetamido)benzophenone (**2m**) in 15 ml of DMSO was added 1.3 g (10 mmol) of N-(2-aminoethyl)morpholine. The mixture was allowed to stand at room temperature for 15 h and then diluted with water. The resulting mixture was extracted twice with benzene, and the extracts were combined, washed with water, dried, and evaporated. The residue was crystallized from EtOH–petroleum benzin to give 1.34 g (75%) of a *syn* and *anti* mixture of **4o**, mp 89—90°C.

5-Chloro-2-trichloroacetamidobenzophenone Methylimine (5a)——Method C: To a solution of 4.89 g (20 mmol) of **4a** (*syn* and *anti* mixture) and 2.2 g (22 mmol) of triethylamine in 100 ml of benzene was added dropwise 4.0 g (22 mmol) of CCl_3COCl at 10—20°C. The mixture was stirred at room temperature for 2 h and then washed with water. The benzene layer was dried and concentrated to dryness under reduced pressure. Recrystallization of the residue from iso-PrOH afforded yellow crystals which were shown by TLC to contain a considerable amount of quinazolinone **6a**. The crystals were then dissolved in CH_2Cl_2 and an insoluble white solid was filtered and washed with CH_2Cl_2 to give 0.64 g of **6a**. The CH_2Cl_2 solution was evaporated *in vacuo* and the residue was recrystallized from $CHCl_3$–MeOH to give 4.26 g (55%) of **5a** as light yellow plates showing only one spot on TLC ($CHCl_3$ as a developer), melting at 133—134°C. On further raising the temperature, the material soon solidified and finally decomposed at 247—250°C. The filtrate from the second crystallization was evaporated and the residue was washed with CH_2Cl_2 and dried to give an additional 0.55 g of **6a** (total yield 15%).

5-Chloro-2-trichloroacetamidobenzophenone 2-Morpholinoethylimine (5k)——Method C_1: To a solution of 344 mg (1 mmol) of *syn*-**4k** and 120 mg (1.2 mmol) of triethylamine in 5 ml of THF was added dropwise 220 mg (1.2 mmol) of CCl_3COCl_3. The mixture was stirred at room temperature for 2 h and then concentrated to dryness under reduced pressure. The residue was partitioned between $CHCl_3$ and water. The $CHCl_3$ layer was dried and evaporated. Crystallization of the residue from EtOH gave 370 mg (76%) of **5k** as light yellow plates, mp 127—128°C.

5-Chloro-2-trifluoroacetamidobenzophenone Methylimine (5p)——A. From **2p**: To a solution of 3.28 g (10 mmol) of 5-chloro-2-trifluoroacetamidobenzophenone (**2p**) and 3.0 g (50 mmol) of AcOH in 30 ml of DMSO was added dropwise with ice-cooling 5.2 g (50 mmol) of 30% (w/w) solution of $MeNH_2$ in EtOH. The mixture was stirred at room temperature for 24 h and then poured into 200 g of ice-water. The resulting mixture was extracted with benzene. The benzene layer was washed with water, dried, and evaporated. The residual solid was recrystallized from EtOH to give 2.01 g (59%) of **5p** as yellow prisms, mp 134—135°C. IR (Nujol mull): 1715 (C=O), 1620 (C=N) cm^{-1}; UV λ_{max}^{EtOH} nm ($\varepsilon \times 10^{-3}$): 236 (30.6), 267 (12.1), 273 (12.2), 321 (4.6); NMR ($CDCl_3$) δ: 3.22 (3H, s, CH_3), 6.98 (1H, d, J=2.5 Hz, 6-H), 7.07—7.62 (6H, m, aromatic), 8.65 (1H, d, J=9 Hz, 3-H), 15.5 (1H, s, D_2O exchangeable, NH). *Anal.* Calcd for $C_{16}H_{12}ClF_3N_2O$: C, 56.40; H, 3.55; Cl, 10.40; N, 8.22. Found: C, 56.26; H, 3.68; Cl, 10.43; N, 8.24.

B. From **4a**: The *syn* and *anti* mixture of **4a** (1.22 g) was trifluoroacetylated according to method C_1 with 1.26 g of $(CF_3CO)_2O$. The residue was recrystallized from EtOH–petroleum benzin to give 0.70 g (41%) of **5p**, mp 133.5—134.5°C.

5-Chloro-2-trifluoroacetamidobenzophenone Ethylimine (5q)——A mixture of 6.55 g (20 mmol) of **2p**, 3.26 g (40 mmol) of $EtNH_2 \cdot HCl$, 5.52 g (40 mmol) of K_2CO_3, 50 ml of DMSO was heated with stirring at 65—70°C for 8 h. The mixture was then worked up as described under method B. Recrystallization from EtOH gave 3.05 g (43%) of **5q** as yellow prisms, mp 112—113°C. IR (Nujol mull): 1705 (C=O), 1615 (C=N) cm^{-1}; UV λ_{max}^{EtOH} nm ($\varepsilon \times 10^{-3}$): 237 (31.8), 267 (12.1), 273 (12.3), 320 (4.7); NMR ($CDCl_3$) δ: 1.27 (3H, t, J= 7.5 Hz, $CH_2\underline{CH_3}$), 3.37 (2H, q, J=7.5 Hz, $\underline{CH_2}CH_3$), 6.93 (1H, d, J=2.5 Hz, 6-H), 7.05—7.60 (6H, m, aromatic), 8.36 (1H, d, J=9 Hz, 3-H), 15.5 (1H, s, NH). *Anal.* Calcd for $C_{17}H_{14}ClF_3N_2O$: C, 57.56; H, 3.98; Cl, 9.99; N, 7.90. Found: C, 57.70; H, 4.04; Cl, 9.91; N, 7.88.

A second crop of 0.43 g (6%), mp 112—113°C, was obtained from the mother liquors.

5-Chloro-2-trifluoroacetamidobenzophenone 3-Morpholinoethylimine (5r)——A. According to method D: A mixture of 3.28 g (10 mmol) of **2p**, 30 ml of DMSO, and 1.56 g (12 mmol) of N-(2-aminoethyl)morpholine was stirred at room temperature for 24 h. The mixture was poured into 200 ml of ice-water, and the solid precipitated was collected by filtration, washed with water, and dried. Recrystallization from $CHCl_3$–EtOH gave 3.77 g (86%) of **5r** as light yellow plates, mp 151—152°C. *Anal.* Calcd for $C_{21}H_{21}ClF_3N_3O_2$: C, 57.34; H, 4.81: Cl, 8.06; N, 9.55. Found: C, 57.29; H, 4.75; Cl, 8.06; N, 9.48.

B. From *syn*-**4k**: Trifluoroacetylation of *syn*-**4k** (1.03 g) according to method C_1 with 0.76 g of $(CF_3CO)_2O$ gave, after recrystallization, 0.91 g (69%) of **5r**, mp 149—150.5°C.

C. From *anti*-**4k**: Treatment of *anti*-**4k** in the same manner as described above (B) gave 0.81 g (61%) of **5r**, mp 150—151°C, identical with that prepared above.

Reaction of 2a with Amines (Table I)——5-Chloro-2-trichloroacetamidobenzophenone imines (**5a—l**, Table II) and/or 6-chloro-3,4-dihydro-4-phenyl-4-trichloromethyl-2(1*H*)-quinazolinones (**6a—c, f—l**, Table III) were obtained according to the following methods.

Method D: A solution of 3.77 g (10 mmol) of **2a** and 12 mmol of an amine in 20 ml of DMSO was stirred at room temperature for 20 h and then poured into 200 ml of ice-water. The precipitate that formed was collected by filtration, washed successively with water and isopropyl ether (IPE), and dried.

Method D_1: To a solution of 3.77 g (10 mmol) of **2a** in 20 ml of DMSO were added 40 mmol each of an amine hydrochloride and triethylamine. The mixture was stirred at room temperature for 20 h and then worked up as described under method D.

Method D_2: The reaction of 3.77 g of **2a** with isopropylamine was carried out as described under method D, but TLC showed that a considerable amount of **2a** still remained. Accordingly, 18 mmol more of isopropylamine was added, and the mixture was stirred at room temperature for an additional 25 h. Work-up as described under method B and recrystallization from $CHCl_3$–EtOH gave 3.17 g (76%) of **5d**.

Method D_3: A stirred mixture of 1.89 g (5 mmol) of **2a**, 1.0 g (10 mmol) of cyclohexylamine, and 10 ml of DMSO was heated at 60°C for 6 h and then worked up as described under method D_2.

Method E: A stirred mixture of 1.89 g (5 mmol) of **2a**, 0.59 g (10 mmol) of *n*-propylamine, and 20 ml of EtOH was heated at 60°C for 3 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc. The solution was washed with water, dried, and concentrated.

Method E_1: The reaction was carried out as described under method E, but under reflux.

Method F: The reaction was carried out as described under method E, but under gentle reflux in THF for 8 h.

Method G: A solution of 1.14 g (6 mmol) of $TiCl_4$ in 10 ml of benzene was added dropwise to a solution of 3.77 g (10 mmol) of **2a** and 45 mmol of an amine in 50 ml of benzene at 5—10°C with ice-cooling under nitrogen atmosphere. The mixture was stirred at room temperature for 4 h, and the resulting precipitate was removed by filtration and washed with benzene. The filtrate was washed thoroughly with dilute $NaHCO_3$ solution, and the precipitated white solid was filtered off. The benzene layer was washed with water, dried, and evaporated.

Method G_1: The reaction of **2a** with *p*-toluidine was carried out at room temperature for 24 h as described under method G, but TLC showed that about a half of **2a** remained. Accordingly, the mixture was heated at 60°C for 5 h and then worked up as described above.

Method H: A stirred mixture of 3.77 g (10 mmol) of **2a**, 15 mmol of an amine, and 40 ml of benzene

was heated under reflux for 5 h. After cooling, the reaction mixture was washed with water, and insoluble material (compound **6**), if any, was separated by filtration. The benzene solution was dried and evaporated.

Method I: A stirred mixture of 1.89 g (5 mmol) of **2a**, 0.325 g (5.5 mmol) of isopropylamine and 20 ml of HMPT was heated at 100°C for 5 h. After cooling, the mixture was partitioned between benzene and water. The benzene layer was washed with water, dried, and evaporated.

Method I_1: The reaction of 1.89 g (5 mmol) of **2a** with 2.14 g (20 mmol) of *p*-toluidine was carried out for 14 h according to method I.

Acid Hydrolysis of 5a——To a solution of 100 mg of **5a** in 10 ml of benzene was added a mixture of 3 ml of conc. HCl and 5 ml of water. The mixture was stirred and heated under gentle reflux for 1 h. The benzene layer was separated, washed with water, dried, and evaporated. Crystallization of the residue from EtOH–petroleum benzin gave 60 mg (64%) of **2a** as colorless prisms, mp 91—92°C (lit.[1] mp 91—92°C).

Preparation of 6-Chloro-3,4-dihydro-3-methyl-4-phenyl-4-trichloromethyl-2(1*H*)-quinazolinone (6a) from 5a——Method J: A mixture of 195 mg (0.5 mmol) of **5a**, 170 mg (2 mmol) of $NaHCO_3$, and 6 ml of DMF was stirred at room temperature for 4 h and then poured into 50 g of ice-water. The precipitate that formed was collected, washed with water, and dried to give 170 mg (87%) of **6a** as colorless crystals, mp 255°C dec.

Method K: The crystals of **5a** (100 mg) were heated at 150°C for 0.5 h in an electric oven. The solid was then recrystallized from $CHCl_3$ to give 60 mg of **6a**, mp 252°C dec.

6-Chloro-3,4-dihydro-4-phenyl-3-(*n*-propyl)-4-trichloromethyl-2(1*H*)-quinazolinone (6c)——Compound **5c** (210 mg) was treated as described under method J for 24 h. The crude solid was triturated with IPE and insoluble material was collected by filtration, washed with IPE, and dried to give 105 mg (50%) of **6c** as light yellow crystals, mp 237°C dec.

6-Chloro-3,4-dihydro-3-isopropyl-4-phenyl-4-trichloromethyl-2(1*H*)-quinazolinone (6d)——Method L: A mixture of 418 mg of **5d** and 5 ml of pyridine was heated under reflux for 14 h and then poured into ice-water. The resulting mixture was neutralized with dilute HCl, and the precipitate was collected, washed successively with dilute HCl and water, and dried to give 350 mg of crude solid. It was chromatographed on silica gel using $CHCl_3$ to give 190 mg (45%) of **6d**.

Method M: A mixture of 836 mg of **5d** and 10 ml of HMPT was heated at 100°C for 3 h and then poured into ice-water. The precipitate that formed was collected, washed with water, and dried to give 780 mg of crude solid. It was recrystallized from $CHCl_3$–EtOH to give 460 mg of **6d** as colorless needles, mp 249°C dec. A second crop of 76 mg (mp 248°C dec.) was obtained from the mother liquors (total yield 64%).

6-Chloro-3-cyclohexyl-3,4-dihydro-4-phenyl-4-trichloromethyl-2(1*H*)-quinazolinone (6e)——Compound **5e** (2.29 g) was heated for 7 h as described under method M to give 1.53 g (67%) of **6e**. Recrystallization from $CHCl_3$–EtOH gave colorless prisms, mp 247°C dec. IR (Nujol mull): 3340, 3200, 3080, 3050 (NH), 1675 (C=O); NMR ($CDCl_3$–DMSO) δ: 0.3—3.0 (11H, m, cyclohexyl), 6.57 (1H, d, J=2 Hz, 5-H), 6.90 (1H, d, J=8 Hz, 8-H), 7.13—7.57 (5H, m, aromatic), 8.2—8.4 (1H, m, 2′-H), 9.87 (1H, s, NH).

6-Chloro-1-methyl-4-phenyl-2(1*H*)-quinazolinone (3m) and 6-Chloro-3,4-dihydro-1-methyl-4-phenyl-4-trichloromethyl-2(1*H*)-quinazolinone (6m)——A mixture of 1.17 g (3 mmol) of **2m**, 1.16 g (15 mmol) of $AcONH_4$, and 20 ml of DMSO was reacted to give 5-chloro-2-methylaminobenzophenone imine (**4m**) as a crude oil.[2] It was then treated as described under method C with 0.21 g (2.1 mmol) of triethylamine and 0.38 g (2.1 mmol) of CCl_3COCl. The residue was chromatographed on silica gel using CH_2Cl_2 to give 0.07 g (6%) of **2m**, 0.40 g (49%) of **3m**, and 0.39 g (33%) of **6m**. Compound **6m** was recrystallized from EtOH to give colorless prisms, mp 222—223°C. *Anal.* Calcd for $C_{16}H_{12}Cl_4N_2O$: C, 49.28; H, 3.10; Cl, 36.36; N, 7.18. Found: C, 49.34; H, 3.32; Cl, 36.21; N, 7.03.

Compound 3m from 6m——The reaction of 78 mg (0.2 mmol) of **6m** with $NaHCO_3$ was carried out for 2 h as described under method J to give 52 mg (96%) of **3m**, mp 221—222°C, identical with that prepared by the reaction of **2m** with NH_3.[1]

6-Chloro-1-cyclopropylmethyl-4-phenyl-2(1*H*)-quinazolinone (3n) and 6-Chloro-1-cyclopropylmethyl-3,4-dihydro-4-phenyl-4-trichloromethyl-2(1*H*)-quinazolinone (6n)——5-Chloro-2-cyclopropylmethylaminobenzophenone imine (**4n**, 0.57 g) prepared from 5-chloro-2-(N-cyclopropylmethyl-trichloroacetamido)benzophenone (**2n**) was treated as described under method C with 0.21 g of triethylamine and 0.38 g of CCl_3COCl. Chromatography of the residue on silica gel using CH_2Cl_2 gave 0.09 g (16%) of 5-chloro-2-cyclopropylmethylaminobenzophenone (**1n**), 0.11 g (18%) of **3n**, and 0.50 g (58%) of **6n**. Compound **6n** was recrystallized from EtOH to give colorless prisms, mp 221—222°C. IR (Nujol mull): 3210, 3080 (NH), 1670 (C=O) cm^{-1}; UV λ_{max}^{EtOH} nm ($\varepsilon \times 10^{-3}$): 262 (13.0), 304 (2.2); NMR ($CDCl_3$) δ: 0.3—0.5 (4H, m, cyclopropyl CH_2), 0.8—1.3 (1H, m, cyclopropyl CH), 3.9 (2H, d, J=6 Hz, NCH_2), 6.1 (1H, s, NH), 7.04—7.40 (6H, m, aromatic), 7.7—7.9 (2H, m, aromatic). *Anal.* Calcd for $C_{19}H_{16}Cl_4N_2O$: C, 53.05; H, 3.75; Cl, 32.97; N, 6.51. Found: C, 52.83; H, 3.81; Cl, 33.26; N, 6.40.

Compound 3n from 6n——A mixture of 130 mg (0.3 mmol) of **6n** and 140 mg (1 mmol) of K_2CO_3 in 3 ml of dioxane was stirred at room temperature for 2 h. It was then diluted with water and the resulting precipitate was collected, washed with water, and dried to give 90 mg (97%) of **3n**, mp 175—176°C (lit.[1] mp 175—176°C).

Compound 6n from 3n——To a solution of 4.66 g (15 mmol) of **3n** in 30 ml of dioxane was added dropwise a solution of 4.9 g (30 mmol) of CCl_3COOH in 15 ml of dioxane with stirring at 90—95°C and the reaction

mixture was heated under reflux for 15 h. After addition of a further 4.9 g of CCl_3COOH, heating was continued for an additional 9 h. The mixture was then cooled, diluted with water, and neutralized with a saturated $NaHCO_3$ solution. The precipitate was collected, washed with water, and dried to give 6.23 g of crude product, which was chromatographed on silica gel using $CHCl_3$ as an eluent to give 5.17 g (80%) of **6n**. Recrystallization from $CHCl_3$–EtOH gave colorless prisms, mp 222—223°C. The same reaction was carried out in refluxing toluene as described in the literature[7] to give an 8% yield of **6n**.

6-Chloro-3,4-dihydro-1-methyl-3-(2-morpholinoethyl)-4-phenyl-4-trichloromethyl-2(1*H*)-quinazolinone (6o)——The reaction of 3.58 g (10 mmol) of **4o** (*syn* and *anti* mixture) with CCl_3COCl was carried out with heating under reflux for 2 h as described under method C. Recrystallization of the residue from $CHCl_3$–EtOH gave 3.86 g (77%) of **6o** as colorless prisms, mp 189—190°C. *Anal.* Calcd for $C_{22}H_{23}Cl_4N_3O_2$: C, 52.51; H, 4.61; Cl, 28.18; N, 8.35. Found: C, 52.38; H, 4.62; Cl, 28.46; N, 8.49.

1-Acetyl-6-chloro-3,4-dihydro-3-methyl-4-phenyl-4-trichloromethyl-2(1*H*)-quinazolinone (6r)——A mixture of 0.78 g (2 mmol) of **6a** and 20 ml of $(CH_3CO)_2O$ was heated under reflux for 6 h. After evaporation under reduced pressure, the residue was partitioned between CH_2Cl_2 and water. Insoluble material was filtered off and the organic layer was washed with dilute $NaHCO_3$ solution, dried, and evaporated. Chromatography of the residue on silica gel using $CHCl_3$ gave 0.64 g (74%) of **6r**. It was recrystallized from $CHCl_3$–EtOH to give colorless plates, mp 205.5—206.5°C. *Anal.* Calcd for $C_{18}H_{14}Cl_4N_2O_2$: C, 50.04; H, 3.27; Cl, 32.82; N, 6.49. Found: C, 49.93; H, 3.27; Cl, 33.20; N, 6.47.

Deacetylation of 6r——A suspension of 0.432 g of **6r** and 0.28 g of K_2CO_3 in 5 ml of CH_3OH was stirred at room temperature for 4 h. After evaporation of the solvent the residue was triturated with ice-water. Insoluble material was collected by filtration, washed with water, and dried to give 0.374 g (96%) of **6a**, mp 255°C dec.

2-Amino-5-chloro-N-methylbenzhydrylamine (7a)——To a solution of 2.45 g (10 mmol) of **4a** (a mixture of *syn* and *anti* isomers) in 30 ml of THF was added portionwise with ice-cooling 0.38 g (10 mmol) of $LiAlH_4$. The mixture was stirred at room temperature for 2 h and then decomposed with 1 ml of water. The solid that precipitated was removed by filtration and the filtrate was evaporated. The residual oil was chromatographed on silica gel using CH_2Cl_2 to give 2.2 g (89%) of **7a** as a light yellow oil. IR (neat): 3440, 3330, 3280, 3080—2800, 1610, 1490; NMR ($CDCl_3$) δ: 2.38 (3H, s, CH_3), 3.43 (3H, broad s, D_2O exchangeable, NH and NH_2), 4.63 (1H, s, CH), 6.46 (1H, d, $J=9$ Hz, 3-H), 6.87—7.27 (7H, m, aromatic).

5-Chloro-N-methyl-2-trichloroacetamidobenzhydrylamine (8a)——A. From **7a**: To a solution of 1.24 g (5 mmol) of **7a** and 0.5 g (5 mmol) of triethylamine in 20 ml of ether was added dropwise 0.91 g (5 mmol) of CCl_3COCl. The mixture was stirred at room temperature for 3 h and then washed with water. Insoluble material was collected by filtration, washed with ether, and dried to give 0.25 g (18%) of **9a** as colorless fine crystals, mp 223—224°C. The filtrate was evaporated and the residue was chromatographed on silica gel using $CHCl_3$ to give 1.35 g of a light yellow oil. IR (neat): 3320, 3100—2700, 1710 (C=O). Crystallization from IPE–*n*-hexane gave 1.17 g (60%) of **8a** as colorless prisms, mp 115—116°C. IR (Nujol mull): 3320 (NH), 1710 (C=O); NMR ($CDCl_3$) δ: 1.7 (1H, broad s, D_2O exchangeable, NH), 2.47 (3H, s, CH_3), 4.83 (1H, s, CH), 7.0 (1H, d, $J=2.5$ Hz, 6-H), 7.20—7.35 (6H, m, aromatic), 8.32 (1H, d, $J=9$ Hz, 3-H), 13.1 (1H, broad s, D_2O exchangeable, CONH). *Anal.* Calcd for $C_{16}H_{13}Cl_4N_2O$: C, 49.14; H, 3.35; Cl, 36.26; N, 7.17. Found: C, 49.00; H, 3.62; Cl, 36.03; N, 7.28.

B. Method N: To a solution of 195 mg (0.5 mmol) of **5a** in 10 ml of THF was added 20 mg (0.5 mmol) of $NaBH_4$ with ice-cooling. After being stirred at 0—5°C for 1 h, the mixture was decomposed with cold water, neutralized with dilute HCl, and extracted with $CHCl_3$. The organic phase was washed with water, dried, and evaporated. The residue was chromatographed on silica gel using benzene to give 140 mg (71%) of **8a** as a light yellow oil. Crystallization from petroleum benzin gave 95 mg of colorless prisms, mp 115—116°C.

C. The reduction of **5a** (195 mg) was carried out as described under method O. Work-up as described above gave 120 mg (61%) of **8a**, together with 35 mg (26%) of **9a**.

5-Chloro-N-isopropyl-2-trichloroacetamidobenzhydrylamine (8d)——The reduction of **5d** (210 mg) was carried out as described under method O to give 170 mg (81%) of **8d**. Recrystallization from petroleum benzin gave colorless prisms, mp 100—102°C. IR (Nujol mull): 1715 (C=O); NMR ($CDCl_3$) δ: 1.1 (3H, d, $J=6$ Hz, isopropyl CH_3), 1.2 (3H, d, $J=6$ Hz, isopropyl CH_3), 1.7 (1H, broad s, D_2O exchangeable, NH), 2.86 (1H, heptet, isopropyl CH), 5.07 (1H, s, CH), 7.08 (1H, d, $J=2.5$ Hz, 6-H), 7.2—7.5 (6H, m, aromatic), 8.27 (1H, d, $J=9$ Hz, 3-H), 12.7 (1H, broad s, D_2O exchangeable, CONH). *Anal.* Calcd for $C_{18}H_{18}Cl_4N_2O$: C, 51.46; H, 4.32; Cl, 33.75; N, 6.67. Found: C, 51.70; H, 4.11; Cl, 33.65; N, 6.76.

5-Chloro-N-ethyl-2-trifluoroacetamidobenzhydrylamine (8q)——The reduction of 0.71 g (2 mmol) of **5q** with 0.15 g (4 mmol) of $NaBH_4$, as described under method N gave 0.37 g (52%) of **8q** as a colorless oil. Crystallization from *n*-hexane gave an amorphous solid, mp 38—43°C. IR (Nujol mull): 3320 (NH), 1720 (C=O); NMR ($CDCl_3$) δ: 1.20 (3H, t, $J=7.5$ Hz, $CH_2\underline{CH_3}$), 1.5—2.3 (1H, broad s, D_2O exchangeable, NH), 2.5—2.9 (2H, m, $\underline{CH_2}CH_3$), 4.92 (1H, s, CH), 7.03 (1H, d, $J=2.5$ Hz, 6-H), 7.17—7.40 (6H, m, aromatic), 8.28 (1H, d, $J=9$ Hz, 3-H), 13.5 (1H, broad s, D_2O exchangeable, CONH). *Anal.* Calcd for $C_{17}H_{16}ClF_3N_2O$: C, 57.23; H, 4.52; Cl, 9.94; N, 7.85. Found: C, 57.36; H, 4.49; Cl, 9.95; N, 7.82.

General Procedure for the Preparation of 3-Substituted 6-Chloro-3,4-dihydro-4-phenyl-2(1*H*)-quinazolinones (9a—l, t, v, Table IV)——Method O: To a solution of 1 mmol of **6** in 10 ml of DMF was added 76 mg (2 mmol) of $NaBH_4$ with ice-cooling. The mixture was stirred at room temperature for 3 h and then poured into 100 ml of ice-water. After addition of 1 ml of 1 N HCl, the precipitate that formed was collected by filtration, washed with water, dried, and recrystallized.

6-Chloro-3,4-dihydro-3-methyl-4-phenyl-2(1*H*)-quinazolinone (9a)——A. Method O_1: A mixture of 195 mg (0.5 mmol) of **6a**, 20 mg (0.5 mmol) of $NaBH_4$, and 10 ml of THF was heated under reflux for 8 h. Work-up as described under method O and recrystallization from EtOH gave 111 mg (81%) of **9a** as colorless prisms, mp 223—224°C.

B. Method N_1: The reaction of **5a** (195 mg) with $NaBH_4$ was carried out under reflux for 1 h as described under method N. After similar work-up, 102 mg (75%) of **9a** was obtained.

C. Method P: A solution of 196 mg (0.5 mmol) of **8a** in 5 ml of dioxane was heated under reflux for 6 h. After evaporation of the solvent, the residue was recrystallized from EtOH to give 85 mg (62%) of **9a**, mp 223—224°C.

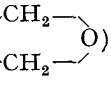
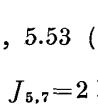
D. From **6r**: The reduction of **6r** (224 mg, 0.5 mmol) was carried out as described under method O to give 136 mg (100%) of **9a**, mp 219—222°C.

E. From **10a**: The reduction of **10a** (160 mg, 0.5 mmol) was carried out for 18 h as described under method O. At that time, TLC indicated that about a half of **10a** remained, so the mixture was heated at 70°C for 3 h. Similar work-up afforded 135 mg (99%) of **9a**, mp 220—223°C.

6-Chloro-3,4-dihydro-1-methyl-4-phenyl-2(1*H*)-quinazolinone (9m)——To a solution of 0.16 g (0.4 mmol) of **6m** in 5 ml of THF was added 0.04 g (1 mmol) of $NaBH_4$. After being stirred at room temperature for 5 h, the mixture was concentrated under reduced pressure. The residue was treated with water and the precipitate was collected, washed with water, and dried to give 0.10 g (92%) of **9m**. Recrystallization from $CHCl_3$–EtOH gave colorless prisms, mp 190—191°, identical with a sample prepared from **3m** by $NaBH_4$ reduction.

6-Chloro-1-cyclopropylmethyl-3,4-dihydro-4-phenyl-2(1*H*)-quinazolinone (9n)——A mixture of 0.13 g (0.3 mmol) of **6n**, 0.02 g (0.5 mmol) of $NaBH_4$, and 5 ml of EtOH was heated under reflux for 1 h. Work-up as described above gave 0.09 g (96%) of **9n**, which was recrystallized from EtOH to give colorless needles, mp 166—167°C. IR (Nujol mull): 3300, 3200, 3080 (NH), 1680 (C=O), 1600 cm^{-1}; NMR ($CDCl_3$) δ: 0.4—0.6 (4H, m, cyclopropyl CH_2), 0.9—1.4 (1H, m, cyclopropyl CH), 3.9 (2H, d, J=6 Hz, NCH_2), 5.5 (1H, s, NCH), 5.7 (1H, broad s, NH), 6.9—7.4 (8H, m, aromatic). *Anal.* Calcd for $C_{18}H_{17}ClN_2O$: C, 69.12; H, 5.48; Cl, 11.33, N, 8.95. Found: C, 69.00; H, 5.42; Cl, 11.33; N, 8.91.

6-Chloro-3,4-dihydro-1-methy -3-(2-morpholinoethyl)-4-phenyl-2(1*H*)-quinazolinone (9o)——A. From **4o**: A mixture of *syn* and *anti* isomers of **4o** (716 mg, 2 mmol) was reduced with $LiAlH_4$ as described for **7a**. Work-up as usual gave 720 mg (100%) of 5-chloro-2-methylamino-N-morpholinoethylbenzhydrylamine (**7o**) as a light yellow oil showing mostly one spot on TLC (5% MeOH in $CHCl_3$ as a developer). IR (neat): 3300 (NH), 3100—2820, 1605, 1585, 1520 cm^{-1}.

The crude amine obtained above was reacted with CCl_3COCl (360 mg, 2 mmol) in benzene as described for **8a**. The reaction mixture was worked up as usual and the residue was chromatographed on silica gel using $CHCl_3$ as an eluent to give 710 mg (92% based on **4o**) of **9o** as a light brown resin, which resisted all attempts at crystallization. IR (neat): 2950—2800, 1655 (C=O), 1600, 1500 cm^{-1}; NMR ($CDCl_3$) δ: 2.30—2.67 (6H, m, CH_2N ), 2.97—4.17 (2H, m, NCH_2), 3.35 (3H, s, NCH_3), 3.57—3.73 (4H, m, ), 5.53 (1H, s, CH), 6.77 (1H, d, J=9 Hz, 8-H), 7.02 (1H, d, J=2 Hz, 5-H), 7.18 (1H, dd, $J_{7,8}$=9 Hz, $J_{5,7}$=2 Hz, 7-H), 7.25 (5H, s, phenyl).

The free base was treated with a slight excess of maleic acid in EtOH. The solution was allowed to cool to give the crystalline quinazolinone **9o** maleate, as colorless prisms.

B. Method Q: To a solution of 558 mg (1.5 mmol) of **9k** in 10 ml of DMF was added with stirring 86 mg (1.8 mmol) of 50% NaH in mineral oil. The mixture was heated at 50—55°C for 1 h, then 284 mg (2 mmol) of methyl iodide was added. The mixture was further heated at 50—55°C for 4 h and then poured into ice-water. The resulting mixture was extracted with benzene and the extracts were washed with water and dried. After evaporation of the solvent the residual oil was chromatographed on silica gel using $CHCl_3$ as an eluent to give 570 mg (98%) of **9o**, identical with that obtained from **4o**.

1-Acetyl-6-chloro-3,4-dihydro-3-methyl-4-phenyl-2(1*H*)-quinazolinone (9r)——Method R: A mixture of 1.36 g (5 mmol) of **9a** and 10 ml of $(CH_3CO)_2O$ was treated and worked up as described for **6r** to give 0.78 g (50%) of **9r**. Recrystallization from EtOH gave colorless needles, mp 128—129°C. *Anal.* Calcd for $C_{17}H_{15}ClN_2O$: C, 64.87; H, 4.81; Cl, 11.27, N, 8.90. Found: C, 64.91; H, 4.82; Cl, 11.40; N, 8.94.

General Procedure for the Preparation of 3-Substituted 4-Alkoxy-6-chloro-3,4-dihydro-4-phenyl-2(1*H*)-quinazolinone (10a—e, Table VI)——Method S: A mixture of 1 mmol of **6**, 280 mg (2 mmol) of K_2CO_3, and 10 ml of an alcohol was heated under reflux for 2 h. After the solvent was evaporated, the residue was triturated with cold water. Insoluble material was collected by filtration, washed with water, and dried.

Method S_1: Compounds **5a** and **5c** were treated as described under method S but with K_2CO_3.

6-Chloro-3,4-dihydro-4-ethoxy-3-isopropyl-4-phenyl-2(1*H*)-quinazolinone (10d)——A stirred mixture of 0.716 g (2 mmol) of **14d** and 20 ml of saturated HCl–EtOH was heated at 60°C for 7 h. After evaporation of the solvent, the residual solid was triturated with dilute Na_2CO_3 solution, collected by filtration, and recrystallized from EtOH to give 0.52 g (75%) of **10d** as colorless needles, mp 216—218°C dec. This product was identical with that prepared from **6d** by method S.

General Procedure for the Preparation of 3-Substituted 6-Chloro-3,4-dihydro-4-hydroxy-4-phenyl-2(1*H*)-quinazolinone (11a—e, j, k, Table VII)——Method T: A mixture of 1 mmol of **6**, 10 ml of DMSO, and 160 mg (1.2 mmol) of 30% NaOH solution was stirred at room temperature for 1 h and then poured into ice-water. The mixture was neutralized with dilute HCl, then the precipitate that formed was collected, washed with water, and dried.

6-Chloro-3,4-dihydro-3-isopropyl-4-hydroxy-4-phenyl-2(1*H*)-quinazolinone (11d)——From **13d**: A mixture of 0.32 g (1 mmol) of **13d**, 5 ml of HMPT, and 0.06 g (1 mmol) of isopropylamine was heated at 100°C for 7 h. After cooling, the mixture was poured into ice-water, and the resulting precipitate was collected by filtration, washed with water, and dried. The crude product was chromatographed on silica gel using $CHCl_3$ as an eluent to give 0.18 g (56%) of **11d** as a yellow oil. Crystallization from benzene–petroleum benzin gave yellow crystals, mp 172—174°C dec. IR (Nujol mull): 3440 (OH), 3380, 3170, 3050 (NH), 1665 (C=O), 1610, 1500 cm^{-1}; NMR ($CDCl_3$–DMSO-d_6) δ: 1.07 (3H, d, J=7 Hz, isopropyl CH_3), 1.47 (3H, d, J=7 Hz, isopropyl CH_3), 3.60 (1H, heptet, J=7 Hz, isopropyl CH), 6.67 (1H, s, D_2O exchangeable, OH), 6.83 (1H, d, J=8 Hz, 8-H), 6.88 (1H, d, J=2 Hz, 5-H), 7.04 (1H, dd, $J_{5,7}$=2 Hz, $J_{7,8}$=8 Hz, 7-H), 7.22—7.63 (5H, m, aromatic), 9.63 (1H, s, D_2O exchangeable, NH).

6-Chloro-3-cyclohexyl-3,4-dihydro-4-hydroxy-4-phenyl-2(1*H*)-quinazolinone (11e)——From **13e**: A mixture of 0.36 g (1 mmol) of **13e**, 5 ml of xylene, and 0.01 ml of phosphorus oxychloride was heated under reflux for 5 h, then chilled, and filtered. The crude product was chromatographed on silica gel using benzene–AcOEt (5: 1) as an eluent to give 0.10 g (28%) of **11e**. Recrystallization from benzene–petroleum benzin gave colorless fine crystals, mp 187—189°C dec. This product was identical (TLC and IR) with that prepared by method T. IR (Nujol mull): 3560 (OH), 3400, 3310, 3200, 1665 (C=O), 1605, 1500 cm^{-1}; NMR ($CDCl_3$–DMSO-d_6) δ: 0.5—1.9 (10H, m, cyclohexyl CH_2), 2.93—3.28 (1H, m, cyclohexyl CH), 6.68 (1H, s, D_2O exchangeable, OH), 6.85 (1H, d, J=8 Hz, 8-H), 6.87 (1H, d, J=2 Hz, 5-H), 7.04 (1H, dd, $J_{5,7}$=2 Hz, $J_{7,8}$=8 Hz, 7-H), 7.23—7.63 (5H, m, aromatic), 9.30 (1H, s, D_2O exchangeable, NH).

5-Chloro-2-ethoxycarbonylaminobenzophenone Isopropylimine (12d)——Compound **5d** (0.836 g, 2 mmol) was treated as described under method S_1 but with EtOH. After evaporation of the solvent, the residue was partitioned between $CHCl_3$ and water. The organic layer was dried and evaporated. Recrystallization of the residue from EtOH gave 0.41 g (59%) of **12d** as colorless plates, mp 126.5—127.5°C. IR (Nujol mull): 1715 (C=O), 1605 (C=N) cm^{-1}; NMR ($CDCl_3$) δ: 1.17 (6H, d, J=6 Hz, isopropyl CH_3), 1.32 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.43 (1H, heptet, J=6 Hz, isopropyl CH), 4.23 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 6.77 (1H, d, J=2.5 Hz, 6-H), 7.0—7.55 (6H, m, aromatic), 8.37 (1H, d, J=9 Hz, 3-H), 13.28 (1H, broad s, D_2O exchangeable, NH). *Anal.* Calcd for $C_{19}H_{21}ClN_2O_2$: C, 66.18; H, 6.14; Cl, 10.28; N, 8.12. Found: C, 66.12; H, 6.18; Cl, 10.35; N, 8.09.

5-Chloro-2-methoxycarbonylaminobenzophenone Cyclohexylimine (12e)——Compound **5e** (0.46 g, 1 mmol) was treated as described above with MeOH to give 0.21 g (57%) of **12e** as colorless plates, mp 143.5—144.5°C after crystallization from MeOH. IR (Nujol mull): 1720 (C=O), 1605 (C=N) cm^{-1}; NMR ($CDCl_3$) δ: 0.93—2.0 (10H, m, cyclohexyl CH_2), 2.97—3.33 (1H, m, cyclohexyl CH), 3.80 (3H, s, CH_3), 6.80 (1H, d, J=2.5 Hz, 6-H), 7.0—7.57 (6H, m, aromatic), 8.42 (1H, d, J=9 Hz, 3-H), 13.4 (1H, s, D_2O exchangeable, NH). *Anal.* Calcd for $C_{21}H_{23}ClN_2O_2$: C, 68.01; H, 6.25; Cl, 9.56; N, 7.55. Found: C, 67.73; H, 6.08; Cl, 9.96; N, 7.67.

1-(2-Benzoyl-4-chlorophenyl)-3-isopropylurea (13d)——From **1a**: A mixture of 4.53 g (20 mmol) of **1a**, 50 ml of dry benzene, and 6.81 g (80 mmol) of isopropyl isocyanate was heated under reflux for 17 h. After cooling, the reaction mixture was washed with water, and the benzene layer was dried and evaporated. Chromatography of the residue on silica gel using benzene as an eluent gave 1.67 g (26%) of **13d**, which was recrystallized from acetone to give colorless plates, mp 193—194°C. IR (Nujol mull): 3330, 3070, 1700, 1660 (C=O), 1600, 1590, 1560, 1515 cm^{-1}. *Anal.* Calcd for $C_{17}H_{17}ClN_2O_2$: C, 64.46; H, 5.41; Cl, 11.19; N, 8.85. Found: C, 64.64; H, 5.57; Cl, 11.17; N, 9.02.

1-(4-Chloro-2-(N-isopropylbenzimidoyl)phenyl)-3-isopropylurea (14d)——A. From **2a**: A mixture of 3.77 g (10 mmol) of **2a**, 20 ml of DMSO, and 1.8 g (30 mmol) of isopropylamine was heated at 100°C for 2 h. Work-up as described under method D gave 1.60 g (45%) of **14d**, which was recrystallized from EtOH to give colorless needles, mp 173—174°C. IR (Nujol mull): 3330, 3170 (NH), 1660 (C=O), 1610 (C=N) cm^{-1}; NMR ($CDCl_3$) δ: 1.17 (6H, d, J=6 Hz, isopropyl CH_3), 1.27 (6H, d, J=6 Hz, isopropyl CH_3), 3.48 (1H, heptet, J=6 Hz, C=NCH), 4.17 (1H, broad s, D_2O exchangeable, 3-NH), 4.62 (1H, heptet, J=6 Hz, CONHC$\underline{H}$), 6.77 (1H, d, J=2.5 Hz, 3-H), 7.03—7.60 (6H, m, aromatic), 8.47 (1H, d, J=9 Hz, 6-H), 13.32 (1H, broad s, D_2O exchangeable, 1-NH). *Anal.* Calcd for $C_{20}H_{24}ClN_3O$: C, 67.12; H, 6.76; Cl, 9.91; N, 11.74. Found: C, 67.30; H, 6.96; Cl, 9.93; N, 11.81.

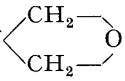
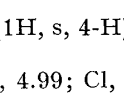
The aqueous filtrate yielded an additional 0.90 g of **14d**, mp 170—172°C (total yield 70%).

B. From **5d**: A mixture of 0.84 g (2 mmol) of **5d**, 5 ml of DMSO, and 0.24 g (4 mmol) of isopropylamine was heated at 100°C for 3 h, and then worked up as described under method D. Recrystallization from EtOH gave 0.42 g of **14d** as colorless needles, mp 173—174°C. An additional 0.14 g (mp 170—172°C) was obtained from the mother liquors (total yield 78%).

1-(4-Chloro-2-(N-cyclohexylbenzimidoyl)phenyl)-3-cyclohexylurea (14e)——A mixture of 3.77 g (10 mmol) of **2a**, 20 ml of DMSO, and 1.98 g (20 mmol) of cyclohexylamine was heated at 100°C for 2 h. After cooling, the mixture was poured into ice-water and the resulting mixture was extracted with AcOEt. The organic layer was washed with water, dried, and evaporated. Crystallization from iso-PrOH–IPE gave 1.77 g (40%) of **14e**. Recrystallization from EtOH gave colorless prisms, mp 159.5—160.5°C. IR (Nujol mull): 3300 (NH), 1660 (C=O), 1603 (C=N) cm^{-1}; NMR ($CDCl_3$) δ: 0.9—2.2 (20H, m, cyclohexyl CH_2), 2.6—3.4 (1H, m, C=NCH), 3.5—4.0 (1H, m, CONHCH), 4.35 (1H, d, J=8 Hz, 3-NH), 6.73 (1H, d, J=2.5 Hz, 3-H), 7.0—7.65 (6H, m, aromatic), 8.42 (1H, d, J=9 Hz, 6-H), 13.1 (1H, s, D_2O exchangeable, 1-NH). *Anal.* Calcd for $C_{26}H_{32}ClN_3O$: C, 71.30; H, 7.36; Cl, 8.09; N, 9.59. Found: C, 71.07; H, 7.36; Cl, 8.15; N, 9.55.

6-Chloro-3,4-dihydro-3-methyl-4-phenyl-2-trifluoromethylquinazoline (15p)——The reduction of **5p** (171 mg) with $NaBH_4$ was carried out as described under method O. Usual work-up and chromatography of the residue on silica gel using $CHCl_3$ gave 118 mg (73%) of **15p** as a colorless solid and 12 mg (10%) of **7a** as a colorless oil. Compound **15p** was recrystallized from EtOH–*n*-hexane to give colorless prisms, mp 105—106°C. IR (Nujol mull): 1620, 1598, 1578, 1190, 1138, 842 cm^{-1}; NMR ($CDCl_3$) δ: 3.0 (3H, s, CH_3), 5.38 (1H, s, 4-H), 6.82 (1H, s, 5-H), 7.18—7.37 (7H, m, aromatic). *Anal.* Calcd for $C_{16}H_{12}ClF_3N_2$: C, 59.18; H, 3.73; Cl, 10.92; N, 8.63. Found: C, 59.11; H, 3.81; Cl, 10.83; N, 8.78.

6-Chloro-3,4-dihydro-3-ethyl-4-phenyl-2-trifluoromethylquinazoline (15q)——A solution of 280 mg (0.78 mmol) of **8q** in 5 ml of dioxane was heated under reflux for 17 h and then concentrated *in vacuo*. Chromatography of the residue on silica gel using benzene as an eluent gave 170 mg (64%) of **15q** as a colorless oil, which was crystallized from petroleum benzin to give colorless plates, mp 79—80°C. IR (Nujol mull): 1615, 1595, 1570 cm^{-1}; NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.95—3.37 (1H, m, $C\underline{H}_aCH_3$), 3.43—3.85 (1H, m, $C\underline{H}_bCH_3$), 5.52 (1H, s, CH), 6.87 (1H, d, J=2.5 Hz, 5-H), 7.07—7.33 (7H, m, aromatic). *Anal.* Calcd for $C_{17}H_{14}ClF_3N_2$: C, 60.28; H, 4.17; Cl, 10.46; N, 8.27. Found: C, 60.17; H, 4.18; Cl, 10.58; N, 8.26.

6-Chloro-3,4-dihydro-3-(2-morpholinoethyl)-4-phenyl-2-trifluoromethylquinazoline (15r)——Compound **5r** (0.88 g) was treated with $NaBH_4$ according to method O to give 0.74 g (87%) of **15r**. Crystallization from iso-PrOH–petroleum benzin gave colorless prisms, mp 100—101°C. IR (Nujol mull): 2830, 1622, 1598, 1580 cm^{-1}; NMR ($CDCl_3$) δ: 2.35—2.70 (6H, m, CH_2N ), 3.0—3.7 (2H, m, NCH_2), 3.60—3.77 (4H, m, N ), 5.75 (1H, s, 4-H), 6.93 (1H, s, 5-H), 7.20—7.38 (7H, m, aromatic). *Anal.* Calcd for $C_{21}H_{21}ClF_3N_3O$: C, 59.51; H, 4.99; Cl, 8.36; N, 9.91. Found: C, 59.51; H, 5.04; Cl, 8.50; N, 9.85.

9-Chloro-10b-phenyl-1,2,3,10b-tetrahydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one (16)——To a solution of 3.77 g (10 mmol) of **2a** in 70 ml of EtOH was added 3.0 g (50 mmol) of ethylenediamine, and the mixture was allowed to stand at room temperature for 20 h, then concentrated *in vacuo*. The residue was diluted with water, and the resulting precipitate was collected by filtration, washed successively with water and cold EtOH, and dried to give 2.3 g (77%) of **16**, mp 271—272°C. Recrystallization from DMF–EtOH gave colorless needles, mp 275—276°C (lit.[10] mp 278—279°C). *Anal.* Calcd for $C_{16}H_{14}ClN_3O$: C, 64.11; H, 4.70; Cl, 11.83; N, 14.02. Found: C, 64.22; H, 4.66; Cl, 12.01; N, 14.04.

9-Chloro-10b-phenyl-2,3,6,19b-tetrahydro-5*H*-oxazolo[3,2-*c*]quinazolin-5-one (17t)——To a solution of 3.77 g (10 mmol) of **2a** in 20 ml of DMSO was added 0.73 g (12 mmol) of monoethanolamine, and the mixture was heated with stirring at 90°C for 2 h. After cooling, the mixture was poured into ice-water and the resulting precipitate was collected, washed with water, and dried to give 2.97 g of crude product. Recrystallization from $CHCl_3$–EtOH gave 2.29 g (76%) of **17t** as colorless prisms, mp 220—222°C (lit.[11] mp 219—220°C). IR (Nujol mull): 3350, 3200, 3100—3050, 1685, 1598 cm^{-1}. NMR ($CDCl_3$) δ: 3.18—3.60 (1H, m, $NC\underline{H}_aH_bCH_2O$), 3.79—4.53 (3H, m, $NCH_a\underline{H}_b\underline{CH}_2O$), 6.97 (1H, d, J=9 Hz, 7-H), 7.20 (1H, dd, $J_{7,8}$=9 Hz, $J_{8,10}$=2 Hz, 8-H), 7.3—7.67 (6H, m, aromatic), 9.93 (1H, s, D_2O exchangeable, NH). *Anal.* Calcd for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; Cl, 11.79; N, 9.31. Found: C, 64.00; H, 4.32; Cl, 11.93; N, 9.43.

6-Chloro-3,4-dihydro-3-(2-hydroxyethyl)-4-phenyl-4-trichloromethyl-2(1*H*)-quinazolinone (6t) and 17t——A mixture of 3.77 g (10 mmol) of **2a**, 1.22 g (20 mmol) of monoethanolamine, and 50 ml of EtOH was heated under reflux for 3 h, and then concentrated to dryness under reduced pressure. The residue was chromatographed on silica gel using $CHCl_3$ as an eluent to give 0.39 g (17%) of **1a**, 1.29 g (43%) of **17t**, and 1.6 g (38%) of **6t**, mp 219—220°C dec. Compound **17t** was recrystallized from $CHCl_3$–EtOH to give colorless prisms, mp 220—222°C, whose NMR spectrum and TLC were identical with those of the crystals obtained above and whose elemental analysis corresponded to formula **17t**; however, the IR spectra in Nujol of both crystals were not fully superimposable. Upon further recrystallization from EtOH, colorless prisms (mp 220—222°C) were obtained, whose IR spectrum was in excellent agreement with that of the crystals prepared previously. Compound **6t** was recrystallized from EtOH to give colorless fine crystals, mp 227—227.5°C

dec. IR (Nujol mull): 3220, 3100, 1672, 1598, 1495 cm^{-1}; NMR ($CDCl_3$) δ: 3.17—4.30 (5H, m, CH_2CH_2OH), 6.83 (1H, d, J=2.5 Hz, 5-H), 6.88 (1H, d, J=9 Hz, 8-H), 7.13—7.60 (5H, m, aromatic), 8.20—8.50 (1H, m, aromatic), 10.07 (1H, s, D_2O exchangeable, NH). *Anal.* Calcd for $C_{17}H_{14}Cl_4N_2O_2$: C, 48.60; H, 3.36; Cl, 33.76; N, 6.67. Found: C, 48.75; H, 3.28; Cl, 33.91; N, 6.56.

Compound 17t from 6t——A mixture of 0.42 g (1 mmol) of **6t**, 0.11 g (2 mmol) of KOH, and 10 ml of EtOH was heated under reflux for 2 h and then worked up as described under method S to give 0.30 g (100%) of **17t**, mp 218—219°C.

10-Chloro-11b-phenyl-3,4,7,11b-tetrahydro-2*H*,6*H*[1,3]oxazino[3,2-*c*]quinazolin-6-one (17u)——Compound **2a** (11.31 g, 30 mmol) was reacted with 4.51 g (60 mmol) of 3-aminopropanol under reflux in EtOH, and the mixture was then treated with 1.7 g (30 mmol) of KOH as described above. After filtration, the filtrate was evaporated and the residue was triturated with water. The resulting solid was collected, washed successively with water and ether, and dried to give 9.25 g (98%) of crude product. Recrystallization from EtOH gave compound **17u** as light yellow prisms, mp 202—203.5°C (lit.[11] mp 202—203°C). *Anal.* Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; Cl, 11.26; N, 8.90. Found: C, 64.58; H, 4.78; Cl, 11.17; N, 8.86.

6-Chloro-3,4-dihydro-3-(2-hydroxypropyl)-4-phenyl-4-trichloromethyl-2(1*H*)-quinazolinone (6v) and 9-Chloro-2-methyl-10b-phenyl-2,3,6,10b-tetrahydro-5*H*-oxazolo[3,2-*c*]quinazolin-5-one (17v)——A mixture of 15.08 g (40 mmol) of **2a**, 4.51 g (60 mmol) of 1-amino-2-propanol, and 100 ml of *n*-PrOH was heated under reflux for 8 h, and then concentrated *in vacuo*. The $CHCl_3$ solution of the residue was washed successively with dilute HCl and $NaHCO_3$ solution, and evaporated. Chromatography of the residue on silica gel using $CHCl_3$ as an eluent gave 2.62 g (28%) of **1a** and 3.85 g (31%) of **17v**. Recrystallization of compound **17v** from iso-PrOH gave colorless plates, mp 221—221.5°C. IR (Nujol mull): 3200, 3080, 3050, 1680, 1600, 1500 cm^{-1}; NMR ($CDCl_3$) δ: 1.38 (3H, d, J=6 Hz, CH_3), 3.45—4.58 (3H, m, NCH_2CHO), 6.83 (1H, d, J=9 Hz, 7-H), 7.10 (1H, dd, $J_{7,8}$=9 Hz, $J_{8,10}$=2.5 Hz, 8-H), 7.20—7.62 (6H, m, aromatic), 9.35 (1H, s, D_2O exchangeable, NH). *Anal.* Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; Cl, 11.26; N, 8.90. Found: C, 64.81; H, 4.72; Cl, 11.18; N, 9.26.

Further elution with AcOEt yielded 6.22 g (36%) of **6v**, which was recrystallized from $CHCl_3$–iso-PrOH to give colorless prisms, mp 241°C dec. IR (Nujol mull): 3580, 3500, 3320, 3200, 3080, 1680, 1600 cm^{-1}. *Anal.* Calcd for $C_{18}H_{16}Cl_4N_2O_2$: C, 49.80; H, 3.72; Cl, 32.66; N, 6.45. Found: C, 49.53; H, 3.71; Cl, 32.65; N, 6.41.

6-Chloro-3,4-dihydro-3-(2-hydroxyethyl)-4-phenyl-2(1*H*)-quinazolinone (9t)——Method U: A mixture of 0.30 g (1 mmol) of **17t**, 0.04 g (1 mmol) of $NaBH_4$, and 10 ml of EtOH was stirred at room temperature for 3 h, and concentrated *in vacuo*. The residue was treated with ice-water and then extracted with $CHCl_3$. The extracts was washed with water, dried, and evaporated to give 0.30 g (99%) of **9t**. Recrystallization from EtOH gave colorless crystals, mp 200—200.5°C, identical with those obtained from **6t** by method O.

6-Chloro-3,4-dihydro-3-(3-hydroxypropyl)-4-phenyl-2(1*H*)-quinazolinone (9u)——The reduction of **17u** (0.32 g) was carried out for 10 h as described under method U. The reaction mixture was concentrated and the residue was treated with ice-water and acidified with dilute HCl. The precipitate was collected, washed with water, and dried to give 0.31 g (98%) of crude product. Recrystallization from EtOH–petroleum ether gave colorless needles, mp 165—166°C. *Anal.* Calcd for $C_{17}H_{17}ClN_2O_2$: C, 64.46; H, 5.41; Cl, 11.19; N, 8.84. Found: C, 64.22; H, 5.32; Cl, 11.33; N, 8.91.

6-Chloro-3,4-dihydro-3-(2-hydroxypropyl)-4-phenyl-2(1*H*)-quinazolinone (9v)——A mixture of 0.62 g (2 mmol) of **17v**, 0.12 g (3 mmol) of $NaBH_4$, and 10 ml of EtOH was stirred at room temperature for 4 h. Work-up as described above gave 0.62 g (98%) of crude product, which was recrystallized from EtOH to give colorless plates, mp 196—199°C.

9-Chloro-6-cyclopropylmethyl-10b-phenyl-2,3,6,10b-tetrahydro-5*H*-oxazolo[3,2-*c*]quinazolin-5-one (17w)

——A. From **17t**: To a stirred solution of 3.61 g (12 mmol) of **17t** in 80 ml of DMF was added portionwise 0.50 g (13 mmol) of 64% NaH, and the mixture was heated at 100°C for 30 min. After cooling, 2.3 g (15 mmol) of 90% cyclopropylmethyl bromide was added and the resulting mixture was heated at 100°C for 5 h. Usual work-up and recrystallization of the crude product from EtOH gave 3.05 g (72%) of **17w** as colorless prisms, mp 143—144°C. IR (Nujol mull): 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ: 0.40—0.70 (4H, m, cyclopropyl CH_2), 0.93—1.40 (1H, m, cyclopropyl CH), 3.27—3.63 (1H, m, $NCH_aH_bCH_2O$), 3.67—4.43 (5H, m, $NCH_aH_bCH_2O$ and NCH_2- ), 7.03 (1H, d, J=9 Hz, 7-H), 7.17—7.63 (7H, m, aromatic). *Anal.* Calcd for $C_{20}H_{19}ClN_2O_2$: C, 67.70; H, 5.40; Cl, 9.99; N, 7.89. Found: C, 67.69; H, 5.46; Cl, 10.14; N, 7.75.

B. From **3n**: A stirred mixture of 5.0 g (16 mmol) of **3n** and 21 g of ethylene carbonate was heated at 190°C for 20 h, and then cooled to 60°C. EtOH (100 ml) and 3 N NaOH solution (300 ml) were successively added dropwise with ice-cooling. The precipitate that formed was collected by filtration, washed with water, and dried. Chromatography of the crude product on a silica gel column eluting with $CHCl_3$ gave 3.74 g (66%) of **17w**, which was recrystallized from iso-PrOH to give colorless fine crystals, mp 141—142°C, identical with those obtained above.

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