[Chem. Pharm. Bull. 26(6)1633—1651(1978)]

UDC 547.856.1.04 : 547.572.04

Synthetic Studies on Quinazoline Derivatives. I. Formation of 2(1H)-Quinazolinones from the Reaction of 2-Trihaloacetamidophenyl Ketones with Ammonia

Michihiro Yamamoto, Shigeho Inaba, and Hisao Yamamoto

Research and Development Center, Pharmaceuticals Division
Sumitomo Chemical Co., Ltd.[1]

(Received August 13, 1977)

A series of 2-trihaloacetamidophenyl ketones was prepared. The 2-trichloro- or 2-tribromoacetamidophenyl ketones, in most cases, were readily converted to the corresponding 4-substituted 2(1H)-quinazolinones by reaction with ammonia *via* loss of the trihalomethyl function. Treatment of 5-chloro-2-trichloroacetamidobenzophenone with ammonium acetate in dimethyl sulfoxide (method H) gave 6-chloro-4-phenyl-2(1H)-quinazolinone in quantitative yield, whereas, under similar conditions, the 2-trifluoroacetamide derivative reacted to yield 6-chloro-4-phenyl-2-trifluoromethylquinazoline. In the case of the N-substituted derivative of 2-trichloroacetamidobenzophenones, the 4-phenyl-2H-3,1-benzoxazin-2-ones or 2-aminobenzophenone imines were isolated depending on the reaction conditions. For the conversion of the N-substituted derivatives to the corresponding 2(1H)-quinazolinones the best result was obtained by heating them with ammonium acetate in dioxane (method J). In the case of the trichloroacetanilides bearing an ethoxycarbonyl, cyano or hydrogen in the *o*-position, the corresponding cyclic or acyclic ureas were obtained by this reaction. Mechanisms for their formations are proposed.

Keywords——trihaloacetylation; 2,2,2-trihaloacetamides; 2-aminobenzophenones; nucleophilic attack of ammonia; cleavage of carbon-carbon bond; ammonolysis; anti-inflammatory drug; 2H-3,1-benzoxazin-2-ones; phenylurea; addition-elimination mechanism

During our investigation of 1,4-benzodiazepines, we unexpectedly found[2] that 5-chloro-2-trichloroacetamidobenzophenone(II-4) reacted with ammonia in methanol at room temperature to give a hardly soluble white crystalline compound having a high melting point, to which we assigned from infrared(IR), and nuclear magnetic resonance(NMR) spectral data and elemental analyses 6-chloro-4-phenyl-2(1H)-quinazolinone (III-4). The structure was confirmed by identification with the sample prepared by the fusion of 2-amino-5-chlorobenzophenone with urea.[3] It had, however, been shown that the 2-haloacetaminobenzophenones II″ (Chart 1) yielded the 1,4-benzodiazepin-2-ones V in the similar reaction conditions.[4] This discovery of the interesting formation of the 2(1H)-quinazolinone by the cleavage of the carbon-carbon bond of trichloroacetyl radical under such mild conditions prompted us to investigate the reaction of the trihaloacetanilides with ammonia.

In the meantime the syntheses and pharmacological properties of 1-alkyl substituted 2(1H)-quinazolinones III were independently reported by Ott *et al.*[5] and Allais *et al.*[6] Since that time a large number of the 2(1H)-quinazolinone compounds have been prepared by a

1) Location: *4-2-1, Takatsukasa, Takarazuka-shi, Hyogo.*
2) S. Inaba, M. Yamamoto, K. Takahashi, K. Mori, K. Ishizumi, and H. Yamamoto, Ger. Offen. 1935404 (1970) [*Chem. Abstr.*, **72**, 90494 (1970)].
3) T.S. Sulkowski and S.J. Childress, *J. Org. Chem.*, **27**, 4424 (1962).
4) L.H. Sternbach, R.I. Fryer, W. Metlesics, E. Reeder, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).
5) H. Ott and M. Denzer, *J. Org. Chem.*, **33**, 4263 (1968); H. Ott, Fr. Patent 1571271 (1969) [*Chem. Abstr.*, **72**, 100739 (1970)].
6) A. Allais and J. Meier, Fr. Patent 1520743 (1968) [*Chem. Abstr.*, **71**, 49975 (1969)].

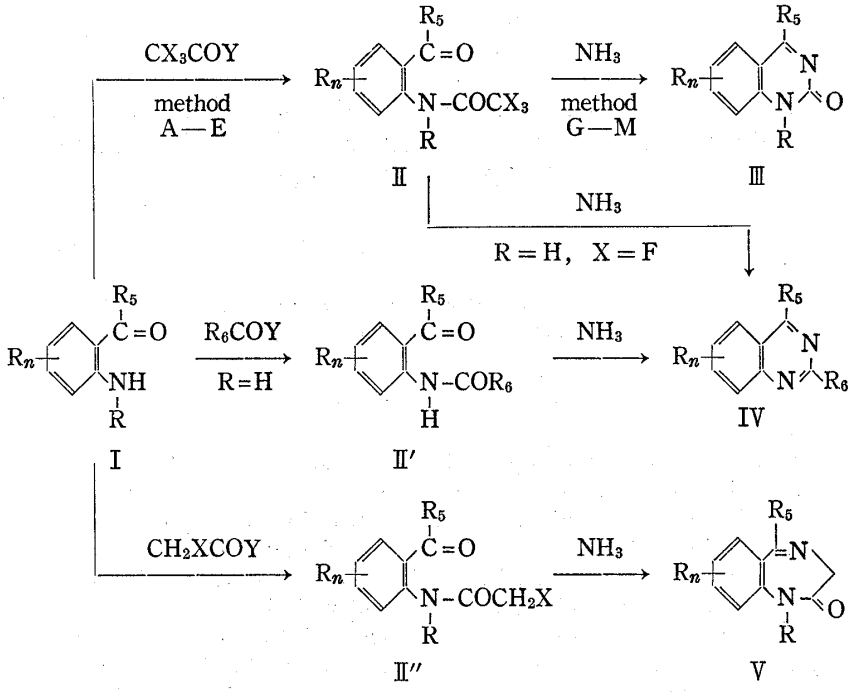


Chart 1

variety of methods and tested for anti-inflammatory and analgesic activities in animals,[7] and a few of them have progressed to clinical trials in humans.[8]

A search of the literature revealed that, in 1893, Bischler and Howell[9] had described the separation of chloroform by heating *o*-trichloroacetamidoacetophenone with alcoholic ammonia without isolation of any other products. The reaction of the N-acyl derivatives of 2-aminophenyl ketones (II') with alcoholic ammonia has, in general, been known as Bischler's synthesis,[10] which can widely be used for the preparation of substituted quinazolines IV.[11]

On the other hand, there have been some reports on the substitution reactions of the trihaloacetyl group with the amino or amido nitrogen, or oxygen, which intermolecularly or intramolecularly led to formation of amides[12] or carbamates[13] *via* split of a haloform. The only reference to the synthesis of the quinazoline ring system by such reaction was that of Sato *et al.*,[14] which described the preparation of 2,4(1H, 3H)-quinazolinediones from 2-tri-

7) *a*) E. Wulfert, P. Bolla, and J. Mathieu, *Chim. Ther.*, **1969**, 257; *b*) T. Komatsu, H. Awata, Y. Sakai, T. Inukai, M. Yamamoto, S. Inaba, and H. Yamamoto, *Arzneim.-Forsch.*, **22**, 1958 (1972); *c*) H. Yamamoto, C. Saito, S. Inaba, H. Awata, M. Yamamoto, Y. Sakai, and T. Komatsu, *ibid.*, **23**, 1266 (1973); *d*) R.V. Coombs, R.P. Danna, M. Denzer, G.E. Hardtmann, B. Huegi, G. Koletar, H. Ott, E. Jukniewicz, J.W. Perrine, E.I. Takesue, and J.H. Trapold, *J. Med. Chem.*, **16**, 1237 (1973).

8) S.L. Wallace, *Arthritis Rheum.*, **18**, 847 (1975); H. Kobayashi, M. Unai, and Y. Kawashima, *Dental Outlook* (Tokyo), **50**, 181 (1977).

9) A. Bischler and F.J. Howell, *Chem. Ber.*, **26**, 1384 (1893).

10) A. Bischler, *Chem. Ber.*, **24**, 506 (1891); W.L.F. Armarego, "The Chemistry of Heterocyclic Compounds," Fused Pyrimidines, Part 1 (Quinazolines), ed. by D.J. Brown, Interscience Publishers, London, 1967, p. 39.

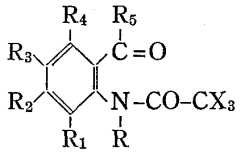
11) W.L.F. Armarego and J.I.C. Smith, *J. Chem. Soc.*, **1966**, 234.

12) *a*) D.M. Bailey and R.E. Johnson, *J. Med. Chem.*, **16**, 1300 (1973); *b*) B. Sukornick, "Organic Syntheses," Vol. 40, ed. by M.S. Newman, John Wiley and Sons, Ltd., New York, 1960, p. 103; *c*) C.A. Panetta and T.G. Casanova, *J. Org. Chem.*, **35**, 4275 (1970).

13) *a*) F. De Marchi and G. Tamagnone, *J. Org. Chem.*, **34**, 1469 (1969); *b*) M.M. Joullie and A.R. Day, *J. Am. Chem. Soc.*, **76**, 2990 (1954); *c*) Y. Iwakura and S. Izawa, *Bull. Chem. Soc. Jpn.*, **39**, 2490 (1966); *d*) H. Bretschneider, K. Hohenlohe-Oehringen, and K. Grassmayr, *Monatsh. Chem.*, **103**, 1523 (1972); *e*) G. Caccia, S. Gladiali, R. Vitali, and R. Gardi, *J. Org. Chem.*, **38**, 2264 (1973).

14) H. Sato, T. Miyadera, M. Fukunaga, T. Tanaka, Y. Kawano, and H. Takagi, Japan Patent 707058 (1970) [*Chem. Abstr.*, **72**, 132775 (1970)].

TABLE I. 2-Trihaloacetamidophenyl Ketones (II)

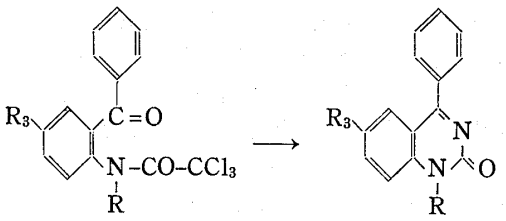


Compd. No.	R	R_1	R_2	R_3	R_4	R_5	X	Method	Yield[a] %	mp, °C	Purification solvent	Formula	Analyses[b]	Starting material[c]
1	H	H	H	H	H	C_6H_5	Cl	A	90	99—100[d]	EtOH	$C_{15}H_{10}Cl_3NO_2$	C, H, Cl, N	a
2	H	Cl	H	H	H	C_6H_5	Cl	B	78	168—169	iso-PrOH-IPE[e]	$C_{15}H_9Cl_4NO_2$	C, H, Cl, N	b
3	H	H	Cl	H	H	C_6H_5	Cl	B	88	135—136	EtOH	$C_{15}H_9Cl_4NO_2$	C, H, Cl, N	c
4	H	H	H	Cl	H	C_6H_5	Cl	A	91	91—92[f]	EtOH	$C_{15}H_9Cl_4NO_2$	C, H, Cl, N	a, b
5	H	H	H	Cl	H	C_6H_5	Br	B	92	113—115	iso-PrOH–DCE[e]	$C_{15}H_9Br_3ClNO_2$	C, H, Br, Cl, N	a, b
6	H	H	H	Cl	H	C_6H_5	F	C	88	126—126.5	EtOH	$C_{15}H_9ClF_3NO_2$	C, H, Cl, N	a, b
7	H	H	H	Br	H	C_6H_5	Cl	B	82	78—79	iso-PrOH	$C_{15}H_9BrCl_3NO_2$	C, H, Br, Cl, N	d
8	H	H	H	F	H	C_6H_5	Cl	B	77	132.5—133.5	iso-PrOH	$C_{15}H_9Cl_3FNO_2$	C, H, Cl, N	b
9	H	Cl	H	Cl	H	C_6H_5	Cl	B	68	217—218	EtOH–$CHCl_3$	$C_{15}H_8Cl_5NO_2$	C, H, Cl, N	d
10	H	H	Cl	Cl	H	C_6H_5	Cl	B	85[g]	113—114	EtOH	$C_{15}H_8Cl_5NO_2$	C, H, Cl, N	d
11	H	H	H	CH_3	H	C_6H_5	Cl	A	81[g]	Oil		$C_{16}H_{12}Cl_3NO_2$	C, H, Cl, N	b
12	H	H	H	OCH_3	H	C_6H_5	Cl	A	83	67.5—68.5	IPE[e]	$C_{16}H_{12}Cl_3NO_3$	C, H, Cl, N	e
13	H	H	O–CH_2–O		H	C_6H_5	Cl	B	75	149—150	iso-PrOH	$C_{16}H_{10}Cl_3NO_4$	C, H, Cl, N	e
14	H	H	NO_2	H	H	C_6H_5	Cl	B	94	136—136.5	iso-PrOH	$C_{15}H_9Cl_3N_2O_4$	C, H, Cl N,	e
15	H	H	H	NO_2	H	C_6H_5	Cl	A[h]	81	121—122[f]	EtOH	$C_{15}H_9Cl_3N_2O_4$	C, H, Cl, N	b
16	H	H	H	H	NO_2	C_6H_5	Cl	B	77[g]	131—132	EtOH	$C_{15}H_9Cl_3N_2O_4$	C, H, Cl, N	e
17	H	H	H	SO_2CH_3	H	C_6H_5	Cl	A[i]	82	158.5—159.5	EtOH	$C_{16}H_{12}Cl_3NO_4S$	C, H, Cl, N, S	b
18	H	H	H	CF_3	H	C_6H_5	Cl	A[i]	85	72—73	EtOH	$C_{16}H_9Cl_3F_3NO_2$	C, H, Cl, N	b
19	H	H	H	$COCH_3$	H	C_6H_5	Cl	A[j]	66	102—103	EtOH	$C_{17}H_{12}Cl_3NO_3$	C, H. Cl, N	b
20	H	H	H	$COOCH_3$	H	C_6H_5	Cl	A[k]	90	137—138	EtOH	$C_{17}H_{12}Cl_3NO_4$	C, H, Cl, N	f
21	H	H	H	CN	H	C_6H_5	Cl	A[l]	88[g]	88—90	iso-PrOH-E[e]	$C_{16}H_9Cl_3N_2O_2$	C, H, Cl, N	f
22	H	H	H	Cl	H	2-ClC_6H_4	Cl	B	82	103—104	EtOH	$C_{15}H_8Cl_5NO_2$	C, H, Cl, N	d
23	H	H	H	Cl	H	3-ClC_6H_4	Cl	B	77	89—90	EtOH	$C_{15}H_8Cl_5NO_2$	C, H, Cl, N	d
24	H	H	H	Cl	H	2-FC_6H_4	Cl	A	90[g]	101—102	EtOH	$C_{15}H_8Cl_4FNO_2$	C, H, Cl, N	b
25	H	H	H	Cl	H	2-$CH_3C_6H_4$	Cl	A[i]	72	92—93	IPE–PE[e]	$C_{16}H_{11}Cl_4NO_2$	C, H, Cl, N	d
26	H	H	H	H	H	CH_3	Cl	A[m]	81	112—113[n]	EtOH	$C_{10}H_8Cl_3NO_2$	C, H, Cl, N	a
27	H	H	H	Cl	H	CH_3	Cl	A	79	85—87	EtOH–PB[e]	$C_{10}H_7Cl_4NO_2$	C, H, Cl, N	e
28	H	H	H	Cl	H	Cyclo-hexyl	Cl	A[l]	74	93—94	EtOH	$C_{15}H_{15}Cl_4NO_2$	C, H, Cl, N	e
29	H	H	H	Cl	H	2-Pyridyl	Cl	A[l]	77	98—98.5	EtOH	$C_{14}H_8Cl_4N_2O_2$	C, H, Cl, N	e
30	H	H	H	Br	H	2-Pyridyl	Cl	A	80	102—103	EtOH–PB[e]	$C_{14}H_8BrCl_3N_2O_2$	C, H, Br, Cl, N	b, e

31	H	H	H	H	H	2-Thienyl	Cl	A	87	101—103	EtOH	$C_{13}H_8Cl_3NO_2S$	C, H, Cl, N, S	g
32	H	H	H	Cl	H	2-Thienyl	Cl	A	86	98—99	EtOH	$C_{13}H_7Cl_4NO_2S$	C, H, Cl, N, S	g
33	H	H	H	Cl	H	2-Furyl	Cl	A[o]	73[g]	80—81	Iso-PrOH	$C_{13}H_7Cl_4NO_3$	C, H, Cl, N	g
34	CH_3	H	H	Cl	H	C_6H_5	Cl	E	87	117—118	EtOH	$C_{16}H_{11}Cl_4NO_2$	C, H, Cl, N	b
35	CH_3	H	H	NO_2	H	C_6H_5	Cl	D	90	120—121	EtOH	$C_{16}H_{11}Cl_3N_2O_4$	C, H, Cl, N	b
36	CH_3	H	H	CH_3	H	Benzyl	Cl	E	89[g]	Oil		$C_{18}H_{16}Cl_3NO_2$	C, H, Cl, N	e
37	C_2H_5	H	H	Cl	H	C_6H_5	Cl	E	85	90—92	EtOH	$C_{17}H_{13}Cl_4NO_2$	C, H, Cl, N	h
38	Iso-C_3H_7	H	H	Cl	H	C_6H_5	Cl	D	66	161—162	EtOH–$CHCl_3$	$C_{18}H_{15}Cl_4NO_2$	C, H, Cl, N	h
39	Allyl	H	H	Cl	H	C_6H_5	Cl	E	88	128—129	EtOH	$C_{18}H_{13}Cl_4NO_2$	C, H, Cl, N	b
40	Benzyl	H	H	Cl	H	C_6H_5	Cl	E	74	84—85	EtOH	$C_{22}H_{15}Cl_4NO_2$	C, H, Cl, N	h
41	CH_2CH_2-OC_2H_5	H	H	Cl	H	2-FC_6H_4	Cl	D	89[g]	44—47	CCl_4–PE[e]	$C_{19}H_{16}Cl_4FNO_3$	C, H, Cl, N	b
42	CH_2CF_3	H	H	Cl	H	C_6H_5	Cl	D	36[g]	133—134	EtOH	$C_{17}H_{10}Cl_4F_3NO_2$	C, H, Cl, N	i, j
43	CH_2CF_3	H	H	OCH_3	H	C_6H_5	Cl	D	50	116—119	iso-PrOH	$C_{18}H_{13}Cl_3F_3NO_3$	C, H, Cl, N	e, j
44	CH_2- 	Cl	H	H	H	C_6H_5	Cl	D	76[g,p]	81—82	CH-H[e]	$C_{19}H_{15}Cl_4NO_2$	C, H, Cl, N	h
45	CH_2- 	H	H	Cl	H	C_6H_5	Cl	E	88	101—102	EtOH	$C_{19}H_{15}Cl_4NO_2$	C, H, Cl, N	b, h
46	CH_2- 	H	H	Cl	H	C_6H_5	Br	B	72[g,q]	106—107	EtOH	$C_{19}H_{15}Br_3ClNO_2$	C, H, Cl, Br, N	b, h
47	CH_2-	H	H	Cl	H	C_6H_5	F	F	70[g]	82.5—83.5	EtOH	$C_{19}H_{15}ClF_3NO_2$	C, H, Cl, N	b, h
48	CH_3- 	H	H	OCH_3	H	C_6H_5	Cl	A[i]	87	104—105	iso-PrOH	$C_{20}H_{18}Cl_3NO_3$	C, H, Cl, N	e
49	CH_2- 	H	H	NO_2	H	C_6H_5	Cl	D	87[g,r]	106—107	EtOH	$C_{19}H_{15}Cl_3N_2O_4$	C, H, Cl, N	h
50	CH_2-	H	H	Cl	H	2-Thienyl	Cl	E	73	88—90	EtOH	$C_{17}H_{13}Cl_4NO_2S$	C, H, Cl, N, S	h

a) Many of these experiments were carried out only once and the optimum conditions were not established.
b) Analyses were within ± 0.4% for the elements indicated.
c) a:commercially available ketones; b: ref. 7*c*, 20*a*; c: ref. 21*a*; d: ref. 21*a*, 22; e:ref. 20*b*, 20*c*; f: L.H. Sternbach, G. Saucy, F.A. Smith, M. Müller and J. Lee, *Helv. Chim. Acta*, **46**, 1720 (1963); g: ref. 21*b*; h: ref.7*c*; i: ref. 23; j: M. Steinman, J.G. Topliss, R. Alekel, W.S. Wong, and E.E. York, *J. Med. Chem.*, **16**, 1354 (1973).
d) F.De Marchi and G.E. Tamagnone, *J. Pharm. Sci.*, **60**, 1757 (1971).
e) IPE:isopropyl ether; DCE: 1,2-dichloroethane; E: ethyl ether; PE:petroleum ether; PB: petroleum benzine; H: *n*-hexane; CH: cyclohexane
f) G.F. Tamagnone and F.De Marchi, *Ann. Chim.* (Rome), **61**, 115 (1971) [*Chem. Abstr.*, **75**, 63709 *g* (1971)].
g) Yield of product isolated after chromatography on silica gel using benzene or CH_2Cl_2 as eluent.
h) CH_2Cl_2 was used as a solvent in this reaction.
i) THF was used as a solvent.
j) $CHCl_3$ was used as a solvent.
k) A mixture of ether and THF was used as a solvent.
l) A mixture of ether and CH_2Cl_2 was used as a solvent.
m) Benzene was used as a solvent.
n) See ref. 9, but melting point was not given.
o) A mixture of ether and $CHCl_3$ was used as a solvent.
p) In addition 3-chloro-2- (N-cyclopropylmethyl-dichloroacetamido) benzophenone (XIa) was isolated in 10% yield, as colorless prisms (from iso-PrOH–IPE), mp 148.5—149°. *Anal.* Calcd. for $C_{19}H_{16}Cl_3NO_2$: C, 57.53; H, 4.07; N, 3.53; Cl, 26.81. Found: C, 57.41; H,4.20; N, 3.88; Cl, 26.48.
q) In addition 5-chloro-2-(N-cyclopropylmethyl-dibromoacetamido)benzophenone (XIb) was isolated in 14%yield, as colorless plates (from EtOH), mp 132—133°. *Anal.* Calcd. for $C_{19}H_{16}Br_2ClNO_2$: C, 46.99; H, 3.32; N, 2.88; Br, 32.91; Cl, 7.30.Found: C, 47.36; H, 3.43; N, 2.81; Br, 32.59; Cl, 7.25.
r) In addition 2-(N-cyclopropylmethyl-dichloroacetamido)-5-nitrobenzophenone (XIc) was isolated in 7% yield, as yellow prisms (from EtOH), mp 131—132°. *Anal.* Calcd. for $C_{19}H_{16}Cl_2N_2O_4$: C,56.04; H, 3.96; Cl, 17.41; N, 6.88;. Found: C, 56.06; H, 3.91; Cl, 17.68; N, 6.92.

TABLE II. Reaction of 2-Trichloroacetamidobenzophenone with Ammonia in Various Conditions



II III

Expt. No.	Source of Ammonia (mol ratio to II)	Solvent[a]	Reaction temp., °C	Reaction time, hr	Yield[b] %	Note
		A. II-4 ⟶ III-4 (R=H; R_3=Cl)				
1	NH_3 (5)	MeOH	r.t.	24	41	c)
2	$AcONH_4$ (8)	EtOH	Reflux	10	63	d)
3	NH_4OH (8)	Dioxane	60	5	61	e)
4	$AcONH_4$ (6)	Dioxane	90	18	66	e)
5	$AcONH_4$ (5)	DMSO	r.t.	24	99	f)
6	NH_4HCO_3 (4)	HMPT	100	2	97	g)
		B. II-15 ⟶ III-13 (R=H, R_3=NO_2)				
7	NH_3 (20)	EtOH	r.t.	24	0	h)
8	NH_3 (20)	*t*-BuOH	r.t.	18	36	d)
9	$AcONH_4$ (10)	*t*-BuOH	Reflux	16	78	d)
10	$AcONH_4$ (6)	Dioxane	Reflux	20	75	e)
11	$AcONH_4$ (6)	CH_3CN	60	18	57	e)
12	$AcONH_4$ (5)	DMSO	r.t.	24	45	d)
13	$HCOONH_4$ (2)	DMSO	60	2	76	d)
14	NH_4HCO_3 (4)	DMSO	60	7	71	d)
15	NH_4HCO_3 (4)	HMPT	100	4	85	g)
16	$AcONH_4$ (2)	HMPT	100	3	87	d)
		C. II-34 ⟶ III-32 (R=CH_3: R_3=Cl)				
17	NH_3 (20)	MeOH	r.t.	72	6[i]	j)
18	NH_3 (20)	EtOH	r.t.	24	25	k)
19	$AcONH_4$ (10)	*t*-BuOH	Reflux	12	58	l)
20	$AcONH_4$ (5)	Dioxane	90	7	91	m)
21	$AcONH_4$ (5)	DMSO	r.t.	24	36[i]	n)
		D. II-35⟶III-33 (R=CH_3: R_3=NO_2)				
22	NH_3 (2)	*t*-BuOH	r.t.	48	15	d)
23	$AcONH_4$ (10)	*t*-BuOH	Reflux	6	80	d)
24	$AcONH_4$ (5)	Dioxane	90	2	89	m)
25	$AcONH_4$ (5)	DMSO	r.t.	4	17[i]	o)

a) DMSO: dimethyl sulfoxide, HMPT: hexamethylphosphoric triamide.
b) Yields of crude products finally washed with an appropriate organic solvent, unless otherwise stated. These products were nevertheless essentially pure by TLC. Washing solvent employed were benzene (expt. 1), ether(expt. 2, 11, 16, 19), isopropyl ether(expt. 3, 4, 18, 20), CH_2Cl_2 (expt. 8, 12, 13,14), EtOH (expt. 9, 10), $CHCl_3$ (expt. 22), and EtOAc(expt. 23, 24).
c) See method G.
d) The filtrate was shown by TLC to contain mostly the corresponding 2-aminobenzophenone I.
e) The filtrate was shown by TLC to contain the unchanged starting material II and the corresponding benzophenone I.
f) See method H.
g) See method I.
h) The crude solid was finally washed well with hot water and dried to give 2-amino-5-nitrobenzophenone quantitatively. The aqueous washing was cooled to give trichloroacetamide as colorless plates, mp 140—141° (lit.[13b] 140—141°).
i) Yield of product isolated after chromatography.
j) Compound VIa was obtained as a main product in 71% yield. See experimental section.
k) Chromatography of the filtrate yielded 38% of Ia, 8% of II-34, 26% of VIb, and 1% of VIIb in the order separated. VIb melted at 82—83° after crystallization from iso-PrOH *Anal.* Calcd. for $C_{17}H_{16}ClNO_3$: C, 64.26; H, 5.08; Cl, 11.16; N, 4.41. Found: C, 64.12; H, 5.13; Cl, 11.19; N, 4.58.
l) The filtrate was shown by TLC to contain mostly the starting material II.
m) See method J_2.
n) The reaction mixture was shown by TLC to contain VIIIa besides III-32. See experimental section.
o) The remaining product isolated by chromatography was only 2-methylamino-5-nitrobenzophenone.

chloroacetamidobenzamide. We now wish to report our synthesis of the 2(1H)-quinazolinones III by the reaction of the 2-trihaloacetamidophenyl ketones II with ammonia.

The ketones II (Table I) were prepared by acylation of the starting 2-aminophenyl ketones I with trihaloacetic acids or their reactive derivatives (methods A—E) with the exception of II-47 (method F). A few of them were known in the literatures as indicated in Table I. Their IR spectra (Nujol mull) exhibited characteristic amide carbonyl bands at 1710—1730 cm^{-1} (R=H) or at 1670—1700 cm^{-1} (R≠H), as well as ketone carbonyl bands at 1640—1650 cm^{-1} (R=H) or at 1660—1680 cm^{-1} (R≠H). NMR spectra of the compounds II (R=H) in deuteriochloroform showed the signal belonging to the proton on C-3 in the 2-aminophenyl moiety in the range of from δ 8.5 (II-12) to 8.9 (II-15), which indicates the existence of intramolecular hydrogen bonding.[15]

The reaction of these compounds with ammonia was extensively studied and found to be more complicated than had been expected as shown in Table II. The reaction of 5-nitro-2-trichloroacetamidobenzophenone (II-15) with ethanolic ammonia at room temperature did not yield the desired 2(1H)-quinazolinone III, but instead produced the deacylated aminobenzophenone I and trichloroacetamide in almost quantitative yields (expt. 7), whereas II-4 yielded the quinazolinone III-4 under similar conditions as mentioned in the introductory part. The structures of these products were confirmed by their comparison of the IR spectra with authentic samples, respectively. When II-15 was reacted in *tert*-butanol, 6-nitro-4-phenyl-2(1H)-quinazolinone (III-13) was isolated in 36% yield along with the deacylated benzophenone (expt.8).

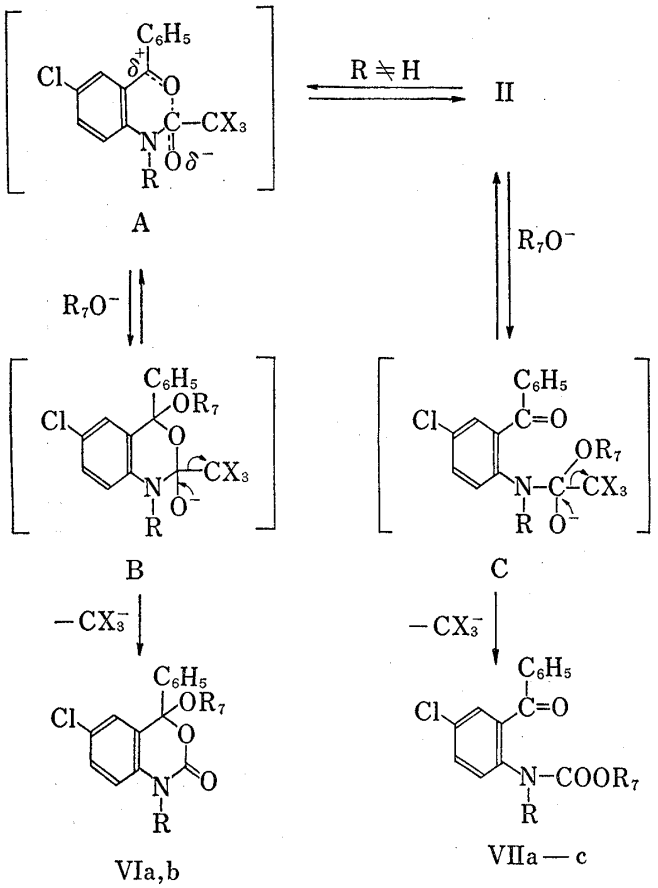


Chart 2

In contrast to II-4, the N-methylated benzophenone II-34 gave, on treatment with ammonia in methanol as well as in ethanol, 6-chloro-1,4-dihydro-4-alkoxy-1-methyl-4-phenyl-2H-3,1-benzoxazin-2-one (VI) as a major product and 5-chloro-2-(N-methyl-alkoxycarbonylamino) benzophenone (VII) as a minor product besides the expected quinazolinone III-32 and 5-chloro-2-methylaminobenzophenone (Ia) (expt. 17 and 18). The structures of VI were suggested by spectral data and microanalyses, and they were, in fact, easily hydrolyzed to Ia on heating with alkali in aqueous alcohol. The structures of VII were established by their identification with the products prepared from Ia and either methyl chlorocarbonate or ethyl chlorocarbonate. In the conversion of II to the benzoxazinone VI and the carbamate VII, ammonia is assumed to act as a simple base. The mechanism of the reaction may be explained as follows (Chart 2). In the case of the non-hydrogen bonded compound II (R≠H), the formation of a six-membered

15) A. Walser, A. Szente, and J. Hellerbach, *J. Org. Chem.*, **38**, 449 (1973).

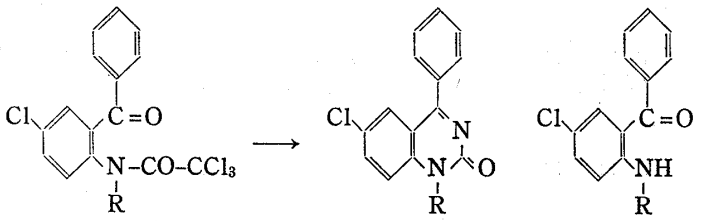
ring transition state A would facilitate a nucleophilic attack by an alkoxide ion on the keto carbonyl to give intermediate B, which may eliminate haloform to yield the benzoxazinone VI. On the other hand, an attack of the alkoxide ion on the amide carbonyl would give intermediate C, which may result in the formation of the carbamate VII *via* split of haloform.

Since the conversion of II to III in alcoholic ammonia was not performed effectively, we further explored the reaction conditions in order to obtain an optimum yield of each of the four representative compounds (Table II).

In view of the results above obtained, ammonia in alcohol was apparently a strong enough base to occur cleavage of the amide bond of II, particularly in case R_3=NO_2. Thus, we attempted to use ammonium salt, which could readily generate ammonia, in place of ammonia itself in order to effect the reaction rather under approximately neutral conditions. For this purpose, ammonium acetate was found to bring about good results. When compounds II-15, II-34 and II-35 were respectively treated with ammonium acetate in *tert*-butanol, the corresponding quinazolinones were obtained in more than two times higher yields than with ammonia base (expt. 9, 19 and 23; method L).

Concerning solvent effects, the use of protic solvents such as methanol and ethanol was not so satisfactory that we then examined aprotic polar solvents. When II-4 was allowed to react with ammonium acetate in dimethyl sulfoxide (DMSO), a quantitative yield of the desired compound III-4 was obtained (expt. 5; method H). When, however, compounds II-15, II-34 and II-35 were subjected to the same conditions, the corresponding quinazolinones were produced in considerably lower yields (expt. 12, 21 and 25). In the preparation of the quinazolinone III-13, the best result was obtained by effecting the reaction of II-15 with ammonium acetate in hexamethylphosphoric triamide (HMPT) (expt. 16). Ammonium formate and ammonium bicarbonate also gave good results in DMSO (expt. 13 and 14). As expected, excellent yields of both III-4 and III-13 were obtained on heating at 100° either II-4 or II-15 with ammonium bicarbonate in HMPT (expt. 6 and 15; method I). For the N-substituted trichloroacetamidobenzophenones, dioxane was found to be a prominent reaction solvent. On treatment of II-34 as well as II-35 with ammonium acetate in dioxane at 90°, the corresponding quinazolinones were obtained in about 90% yields (expt. 20 and 24).

Table III. Reaction of 2-(N-Substituted trichloroacetamido)-5-chlorobenzophenone with Ammonium Acetate at 90—95° in Dioxane

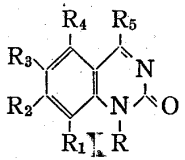


II III I

R	Reaction time[a] hr	Yield,[b] % III	I	Recovery %
CH_2CF_3	1	92	6	0
Benzyl	4	96	3	1
Allyl	6	90	3	3
CH_2- 	7	84	14	1
CH_3	7	92	5	1
C_2H_5	7	95	4	1
Iso-C_3H_7	24	25	25	49

a) The elapsed time before beginning the separation procedure.
b) Yield after chromatography. See method J.

TABLE IV. 2(1H)-Quinazolinones (III)



Compd. No.	R	R_1	R_2	R_3	R_4	R_5	Method[a]	Yield[b] %	mp, °C	Purification solvent[c]	Formula	Analyses[d]	Lit.mp, °C
1	H	H	H	H	H	C_6H_5	H[e]	82	261—263	EtOH	$C_{14}H_{10}N_2O$	C, H, N,	255—256[f]
2	H	Cl	H	H	H	C_6H_5	H_2	100	262—264	DMF	$C_{14}H_9ClN_2O$	C, H, Cl, N	
3	H	H	Cl	H	H	C_6H_5	H_2	100	284—285	DMF	$C_{14}H_9ClN_2O$	C, H, Cl, N	286—287[g]
4	H	H	H	Cl	H	C_6H_5	H[h]	99	321—323	DMF	$C_{14}H_9ClN_2O$	C, H, Cl, N	312[i]
							H_1[j,k]	92					
5	H	H	H	Br	H	C_6H_5	H_1	100	324—326	DMF	$C_{14}H_9BrN_2O$	C, H, Br, N	
6	H	H	H	F	H	C_6H_5	H_1	100	282—283	DMF	$C_{14}H_9FN_2O$	C, H, N,	
7	H	Cl	H	Cl	H	C_6H_5	H_1[e,l,m]	99	330—331	DMF	$C_{14}H_8Cl_2N_2O$	C, H, Cl, N	333—334[g]
8	H	H	Cl	Cl	H	C_6H_5	H_1	100	319—320(dec.)	DMF	$C_{14}H_8Cl_2N_2O$	C, H, Cl, N	
9	H	H	H	CH_3	H	C_6H_5	H_1[k]	96	286—287	DMF	$C_{15}H_{12}N_2O$	C, H, N,	283—285[n]
10	H	H	H	OCH_3	H	C_6H_5	H_3[o]	95	285—286	DMF–$CHCl_3$	$C_{15}H_{12}N_2O_2$	C, H, N,	287[g]
11	H	H	O-CH_2-O		H	C_6H_5	H_2	97	> 360	DMF	$C_{15}H_{10}N_2O_3$	C, H, N,	
12	H	H	NO_2	H	H	C_6H_5	H	100	300—301(dec.)	DMF	$C_{14}H_9N_3O_3$	C, H, N,	
							G[p]	37					
13	H	H	H	NO_2	H	C_6H_5	I[h]	85	314—315	DMF	$C_{14}H_9N_3O_3$	C, H, N	
14	H	H	H	H	NO_2	C_6H_5	H_4	92	312—313(dec.)	DMF	$C_{14}H_9N_3O_3$	C, H, N	
15	H	H	H	SO_2CH_3	H	C_6H_5	H_1	96	> 360	DMF–EtOH	$C_{15}H_{12}N_2O_3S$	C, H, N, S	378[g]
16	H	H	H	CF_3	H	C_6H_5	H_1	93	226—227	EtOH–$CHCl_3$	$C_{15}H_9F_3N_2O$	C, H, N	229[g]
17	H	H	H	$COCH_3$	H	C_6H_5	H_1[q]	81	266—267	EtOH	$C_{16}H_{12}N_2O_2$	C, H, N	
18	H	H	H	$COOCH_3$	H	C_6H_5	H	99	285—287	DMF	$C_{16}H_{12}N_2O_3$	C, H, N	
19	H	H	H	CN	H	C_6H_5	H_1	81	339—341	DMF–$CHCl_3$	$C_{15}H_9N_3O$	C, H, N	
20	H	H	H	Cl	H	2-ClC_6H_4	H_1[k]	79	330—332	DMF	$C_{14}H_8Cl_2N_2O$	C, H, Cl, N	330[g]
21	H	H	H	Cl	H	3-ClC_6H_4	H_2	100	288—290	DMF	$C_{14}H_8Cl_2N_2O$	C, H, Cl, N	
22	H	H	H	Cl	H	2-FC_6H_4	H_2	99	353—355	DMF	$C_{14}H_8ClFN_2O$	C, H, Cl, N	
23	H	H	H	Cl	H	2-$CH_3C_6H_4$	H_3	77	269—271	DMF	$C_{15}H_{11}ClN_2O$	C, H, Cl, N	267—268[g]
24	H	H	H	H	H	CH_3	L[q]	60	230—232	DMF–EtOH	$C_9H_8N_2O$	C, H, N	230[r]
25	H	H	H	Cl	H	CH_3	H_1	95	> 340	DMF–EtOH	$C_9H_7ClN_2O$	C, H, Cl, N	
26	H	H	H	Cl	H	Cyclohexyl	H	100	269.5—270.5	$CHCl_3$	$C_{14}H_{15}ClN_2O$	C, H, Cl, N	275—277[g]
27	H	H	H	Cl	H	2-Pyridyl	H	98	318—319	DMF–$CHCl_3$	$C_{13}H_8ClN_3O$	C, H, Cl, N	
28	H	H	H	Br	H	2-Pyridyl	H[l]	94	301—303	DMF	$C_{13}H_8BrN_3O$	C, H, Br, N	
29	H	H	H	H	H	2-Thienyl	H_1	94	254—256	DMF–$CHCl_3$	$C_{12}H_8N_2OS$	C, H, N, S	254—257[s]
30	H	H	H	Cl	H	2-Thienyl	H_1	98	345—347	DMF	$C_{12}H_7ClN_2OS$	C,H,Cl,N,S	

31	H	H	H	Cl	H	2-Furyl	H_1[e]	88	341(dec.)	DMF	$C_{12}H_7ClN_2O_2$	C, H, Cl, N	
32	CH_3	H	H	Cl	H	C_6H_5	J_2[h,k]	91	226—227	$CHCl_3$–EtOH	$C_{15}H_{11}ClN_2O$	C, H, Cl, N	220[g]
33	CH_3	H	H	NO_2	H	C_6H_5	J_2[h,q]	89	270—271	DMF	$C_{15}H_{11}N_3O_3$	C, H, N	
34	C_2H_5	H	H	Cl	H	C_6H_5	J_2[k]	91	173—174	EtOH	$C_{16}H_{13}ClN_2O$	C, H, Cl, N	168[g]
35	Iso-C_3H_7	H	H	Cl	H	C_6H_5	J_3	68[t,w]	138—139	MeOH-IPE	$C_{17}H_{15}ClN_2O$	C, H, Cl, N	149—150[f]
36	Allyl	H	H	Cl	H	C_6H_5	J_2[k]	81	184—185	Iso-PrOH	$C_{17}H_{13}ClN_2O$	C, H, Cl, N	190[g]
37	Benzyl	H	H	Cl	H	C_6H_5	J_2[k]	92	179—180	EtOH	$C_{21}H_{15}ClN_2O$	C, H, Cl, N	182[g]
38	CH_2CH_2–OEt	H	H	Cl	H	2-FC_6H_4	J[v]	79[t,w]	152—153	EtOH	$C_{18}H_{16}ClFN_2O_2$	C, H, Cl, N	
39	CH_2CF_3	H	H	Cl	H	C_6H_5	J_2[k]	89	185—186	EtOH	$C_{16}H_{10}ClF_3N_2O$	C, H, Cl, N	
40	CH_2CF_3	H	H	OCH_3	H	C_6H_5	J_1	77[t,x]	157—158	Iso-PrOH	$C_{17}H_{13}F_3N_2O_2$	C, H, N	
41	CH_2– 	Cl	H	H	H	C_6H_5	K	37[t]	164—165	EtOH	$C_{18}H_{15}ClN_2O$	C, H, Cl, N	
42	CH_2– 	H	H	Cl	H	C_6H_5	J_2[k]	79	175—176	Iso-PrOH	$C_{18}H_{15}ClN_2O$	C, H, Cl, N	175—176[y]
							J_2[j,q]	79					
							L	88[t]					
43	CH_2– 	H	H	OCH_3	H	C_6H_5	J_4	79[t,*a]	115—116	EtOAc	$C_{19}H_{18}N_2O_2$	C, H, N	115—116[z]
44	CH_2– 	H	H	NO_2	H	C_6H_5	L	87[t]	172—173	EtOH	$C_{18}H_{15}N_3O_3$	C, H, N	172—173*[b]
45	CH_2– 	H	H	Cl	H	2-Thienyl	L*[c]	60[t,*d]	140—141	EtOH	$C_{16}H_{13}ClN_2OS$	C,H,Cl,N,S	

a) See Experimental. The 2-trichloroacetamidophenyl ketones were used as starting materials, unless otherwise indicated.
b) Yields of crude, but sufficiently pure products, unless otherwise stated.
c) DMF: N,N-dimethylformamide; EtOAc: ethyl acetate; IPE: isopropyl ether.
d) Analyses were within ± 0.4% for the elements indicated.
e) The crude crystals were finally washed with ether.
f) See ref. *7d*.
g) See ref.6.
h) Various reaction conditions were tried for the preparation of this compound. See Table II.
i) See ref. 3.
j) The corresponding 2-tribromoacetamidobenzophenone was used as a starting material.
k) The crude crystals were finally washed with isopropyl ether.
l) In this case 10 mol equiv. of $AcONH_4$ was used.
m) Initially the reaction mixture was left at room temperature for 15hr, but at that time most of the starting material remained (TLC).
n) G. Hanschke, *Chem. Ber.*, **32**, 2021 (1899).
o) In this case 5 mol equiv. of $AcONH_4$ was used.
p) The reaction was carried out for 5hr. The crude solid was finally washed with CH_2Cl_2. From the filtrate 2-amino-4-nitrobenzophenone was obtained in 60% yield by chromatography.
q) The crude crystals were finally washed with EtOAc.
r) See ref. 11.
s) H. Ott, U.S. Patent 3551427 [*Chem. Abstr.*, **77**, 19667 (1972)].
t) Yield of product isolated after chromatography.
u) In addition only 5-chloro-2-isopropylaminobenzophenone was isolated.
v) This reaction was carried out for 5hr.
w) In addition only 5-chloro-2-(2-ethoxyethyl)-2′-fluorophenylbenzophenone was isolated in 11% yield.
x) In addition the starting material (21%) was recovered.
y) See ref. *7c*.
z) See ref. *7b*.
**a*) In addition 2-cyclopropylmethylamino-5-methoxybenzophenone (19%) was isolated.
b*) A. Yoshitake, Y. Makari, K. Kawahara, and M. Endo, *J. Label. Compounds*, **9, 537 (1973).
**c*) This reaction was carried out for 25hr.
**d*) In addition the corresponding aminophenyl ketone (8%) and the unchanged starting material (32%) were isolated.

Subsequently, in order to determine the effect of N-substituents on this reaction, several 2-(N-substituted trichloroacetamido)-5-chlorobenzophenones (II), as listed in Table III, were subjected to react with 5 mol equiv. of ammonium acetate in dioxane at 90—95° (method J). When R=2,2,2-trifluoroethyl, the reaction was accomplished within an hour. When R=benzyl, it required about 4 hr for completion. When R was a lower alkyl such as methyl and ethyl, it required at least 7 hr to bring about complete reaction. These findings show that those substituents which decrease the negative charge on the amide nitrogen of II apparently increase the rate of conversion to III. When, however, R=isopropyl, the reaction rate was significantly slower than that when R=methyl or ethyl, presumably owing to the effect of steric hindrance.

On the other hand, the reaction of the N-unsubstituted benzophenones under similar conditions was considerably slower than that of the N-methylated benzophenones (Table II, expt. 4 and 10). The similar result has been reported by Caccia *et al.*[13e] in the case of β-amino alcohols with ethyl trihaloacetates, and it is assumed to be due to deprotonation at the amide nitrogen.

A large variety of 2(1H)-quinazolinones were prepared according to the above-mentioned methods and modified procedures as shown on Table IV. In this connection, we obserbed substituents effects on this reaction. In contrast to the aforesaid II-15 (R_3=NO_2), under method H compound II-14 (R_2=NO_2) could be converted to the desired quinazolinone III-12 in quantitative yield, and under method G, the yield of III-12 was equivalent to that of III-4 from II-4. However, compound II-16 (R_4=NO_2) required much higher temperature for completion of the reaction (method H_4), presumably mainly owing to the steric effect of a nitro group attached to the *ortho* position to the benzoyl group.

The effect of a substituent at the *para* position (R_3) in the aniline ring was further observed as follows. As shown in Table II, the reaction rate of II-35 (R_3=NO_2) was markedly faster than that of II-34 (R_3=Cl) (expt. 20 and 24). On the other hand, the reaction rate of II-43 and II-48 (both R_3=OCH_3) were much slower than that of II-42 and II-45 (both R_3=Cl) respectively, and high temperature was required for completion of the reaction of II-48 (method J_4). These data show that the electron-attracting substituent increases and the electron-withdrowing substituent decreases the rate of conversion of II to III. We also noted that the substituent at the *ortho* position to the amide group (R_1) decreased the reaction rate significantly, owing to the steric hindrance. For example, in contrast to II-4, compound II-9 hardly reacted under method H although it required only 2 hr for completion at 95—100° (method H_1). Compound II-44 also resisted cyclizing to the desired quinazolinone under method J, and it yielded only 37% of III-41 under more vigorous conditions (method K), whereas II-45 was converted to III-42 in 84% yield under method J. These results show that the rate of the reaction of II with ammonia is markedly dependent upon both the electronic and steric factors.

On the contrary, we observed that the reaction of 2-cyclopropylmethylamino-5-methoxybenzophenone with potassium cyanate in acetic acid was considerably faster than that of 5-chloro-2-cyclopropylmethylaminobenzophenone (Ib),[7c] and moreover 2-methylamino-5-nitrobenzophenone did not interact owing to less electronegativity of the anilino nitrogen.

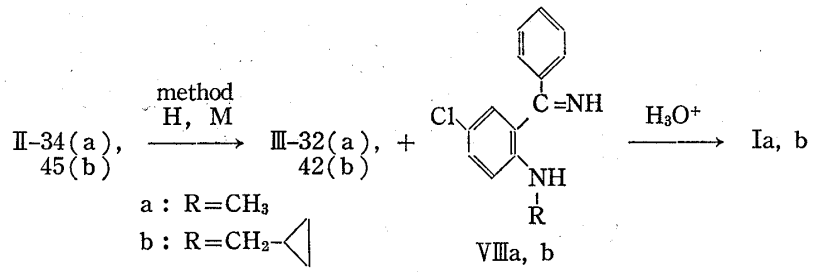


Chart 3

When II-45 was allowed to react with liquid ammonia in an autoclave at room temperature, the quinazolinone III-42 and 5-chloro-2- cyclopropylmethylaminobenzophenone imine (VIIIb) were obtained in a ratio of 1:1 (method M). Reaction of II-45 with ammonium acetate under method H also gave III-42 and VIIIb in a ratio of about 1:2 (Chart 3). Although the reaction of II-34 under method H gave a mixture mostly consisting of the quinazolinone III-32 and 5-chloro-2-methylaminobenzophenone imine (VIIIa), an attempt to isolate the imine VIIIa by chromatography failed because it was readily hydrolysed to Ia through the column.

In the case of treatment of the benzyl ketone II-36 with ammonium acetate in ethanol, the formation of the benzoxazinone IX was observed due to enolization and subsequent intramolecular displacement of chloroform (Chart 4).

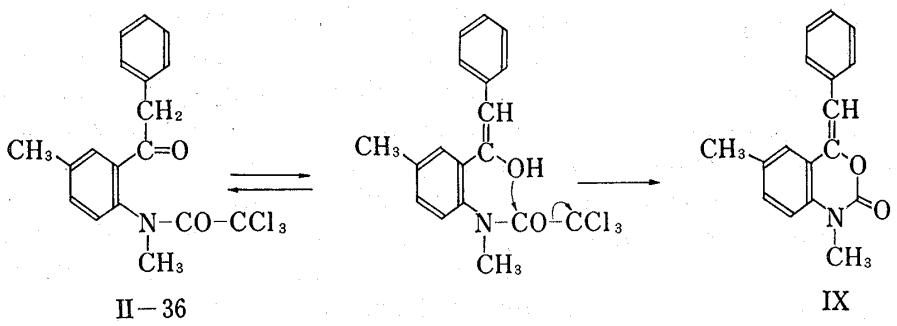


Chart 4

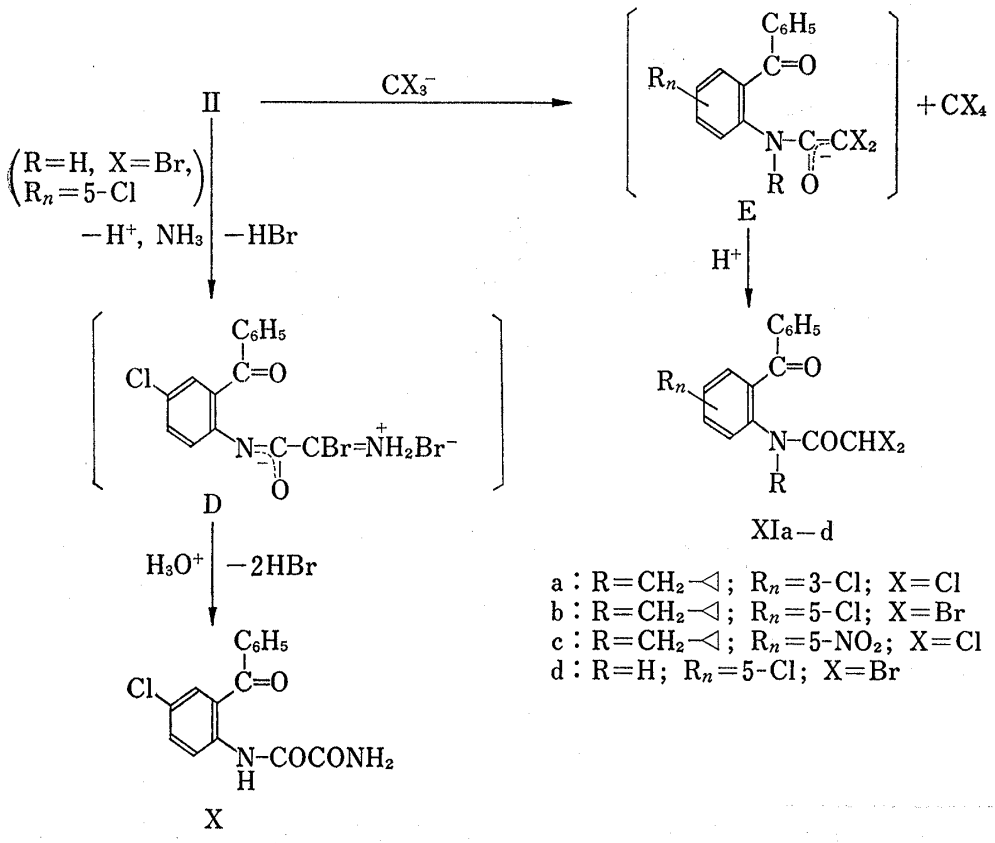


Chart 5

We further investigated the reactivity of the tribromo- and trifluoroacetamidophenyl ketones. In the reaction of II-46 (X=Br) under method J, the yield of III-42 was equivalent to that in the reaction of II-45 (X=Cl). The reaction of II-5 (X=Br) under method H_1 as well as J_1 gave III-4 in good yields, whereas treatment of II-5 with ethanolic ammonia at 90—95° in an autoclave gave a mixture of products, chromatography of which yielded 23% of (2-benzoyl-4-chlorophenyl)oxamide (X) and 14% of 5-chloro-2-dibromoacetamidobenzophenone (XId) besides III-4 (36%) and the carbamate VIIIc (13%). The dihaloacetamidobenzophenones XI were also found to form under methods B, D and K. The following mechanism may account fully for the formation of both products X and XI (Chart 5). If it is assumed that displacement of a bromine atom of II (R=H, X=Br) with ammonia is the first step, the amidobromide D would be formed[16] and subsequent hydrolysis would give the oxamide X. Abstraction of halogen from the trihaloacetyl group by trihalomethyl anion[17] would give rise to the enolate anion E, protonation of which would lead to the dihaloacetanilide XI.

On the other hand, treatment of II-6 (X=F) with ammonia under method G gave only the deacylated aminobenzophenone. Under method H_1, however, it resulted in an almost quantitative conversion to 6-chloro-4-phenyl-2-trifluoromethylquinazoline (IVa). Thus, 5-methyl-2-perfluoropropionamidobenzophenone was also converted to 6-methyl-2-pentafluoroethyl-4-phenylquinazoline (IVb) quantitatively. In the case of the reaction of the N-cyclopropylmethylated derivative II-47 under similar conditions, the 2(1H)-quinazolinone III-42 was produced in low yield, although the major product was the deacylated compound Ib. Under method J, however, II-47 did yield only a trace of Ib. These results support the known fact that the leaving group ability of trifluoromethyl moiety is inferior to that of trichloromethyl group.[12c,13e]

In order to study the further scope of the reaction of the trihaloacetanilides with ammonia, several anilides bearing an ethoxycarbonyl, cyano or hydrogen in the *o*-position instead of

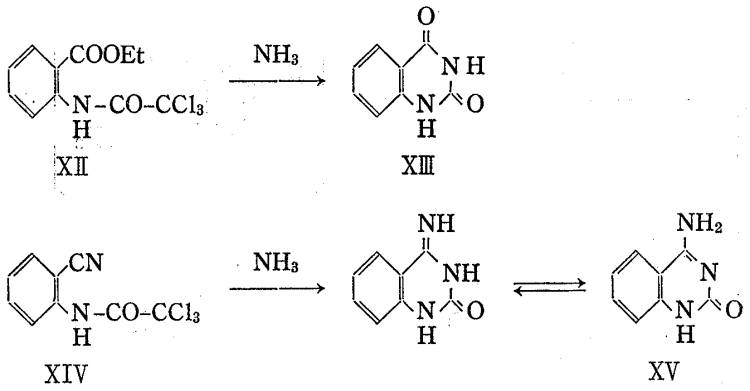
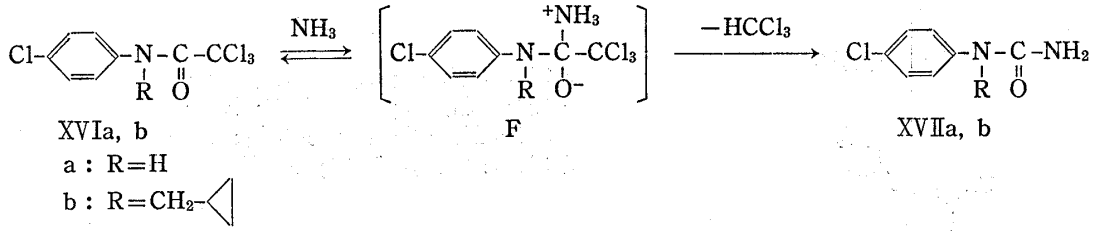


Chart 6



XVIa, b
a : R=H
b : R=CH2-

F

XVIIa, b

Chart 7

16) R. Bonnett, "The Chemistry of the Carbon-Nitrogen Double Bond," ed. by S. Patai, Interscience Publishers, London, 1970, p. 615.
17) W.M. Wagner, H. Kloosterziel, and A.F. Bickel, *Rec. Trav. Chim. Pays-Bas*, **81**, 933 (1962).

an acyl group were prepared. When either ethyl 2-trichloroacetamidobenzoate (XII) or 2-trichloroacetamidobenzonitrile (XIV) (Chart 6) was treated with ammonium acetate under method H, most of the starting material was remained unchanged. On heating at 90—95°, however, both XII and XIV underwent cyclization to the known 2,4 (1H, 3H)-quinazolinedione (XIII) and 4-amino-2(1H)-quinazolinone (XV), respectively. Under similar conditions, 2,2,2,4′-trichloroacetanilide (XVIa) could be converted to 4-chlorophenylurea (XVIIa) in 50% yield. When XVIa was treated with ammonia under method M, the urea XVIIa was obtained in almost quantitative yield. The N-cyclopropylmethyl derivative XVIb also gave N-cyclopropylmethyl-N-(4-chlorophenyl)urea (XVIIb) quantitatively under the same conditions. The formation of the urea is assumed to proceed *via* the tetrahedral intermediate F by the addition-elimination mechanism[18] as shown in Chart 7.

In view of the foregoing discussion, a plausible mechanism for the formation of various kinds of the end products from the reaction of II with ammonia is best represented by the sequence of steps shown in Chart 8. Initial attack of ammonia on the trihaloacetamide

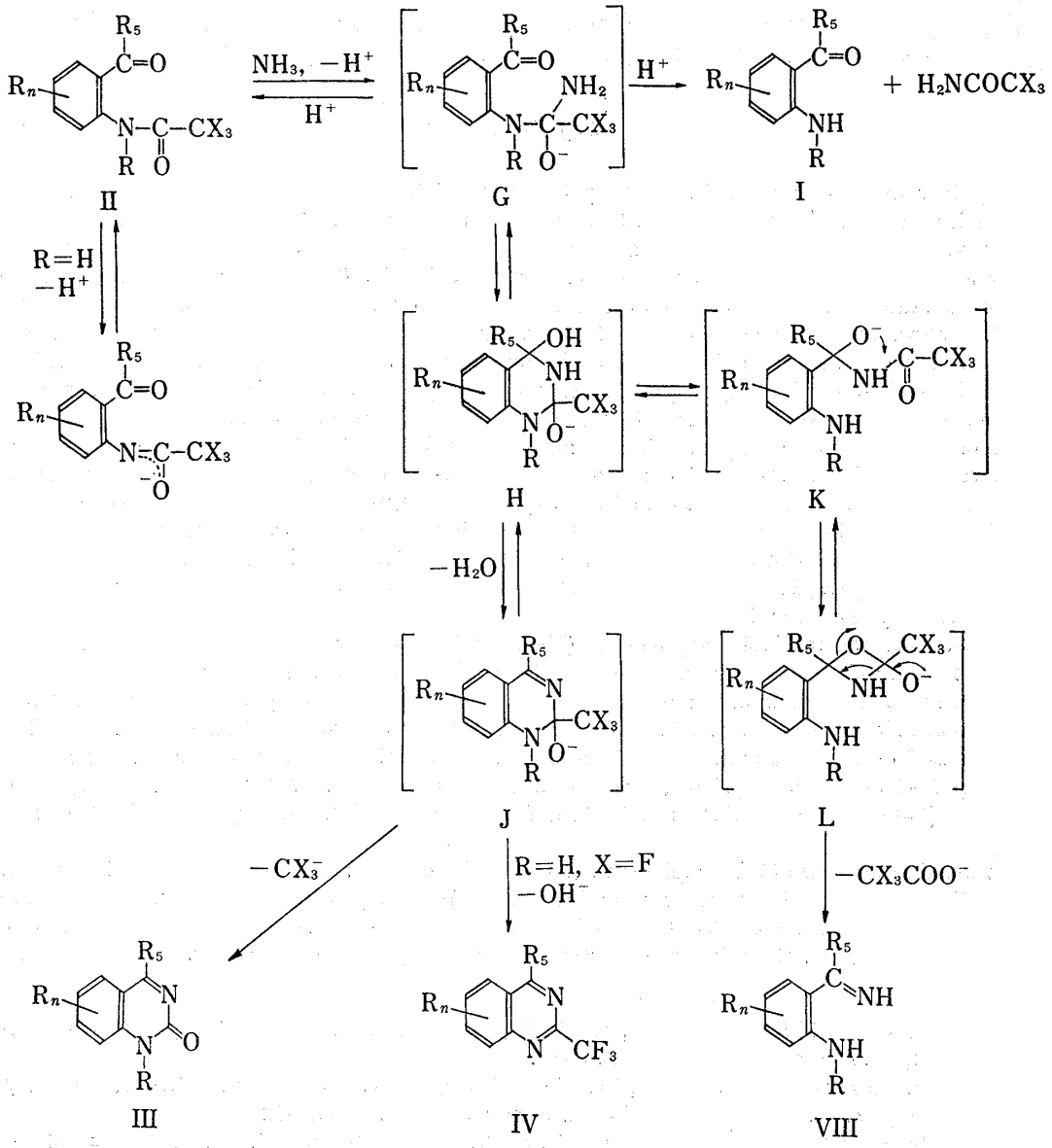


Chart 8

18) A.L.J. Beckwith, "The Chemistry of Amides," ed. by J. Zabicky, Interscience Publishers, London, 1970, p. 109.

carbonyl carbon would give the intermediate G *via* loss of a proton. This might be expected to occur, since the amide carbonyl should be more electrophilic than the keto carbonyl. The addition rate would be accelerated by a lowering of the electron density at the carbonyl carbon but retarded by bulky groups. Subsequent intramolecular attack of the amino nitrogen on the keto carbonyl would give the cyclic carbinolamine H. The amino ketone I together with trihaloacetamide would result from cleavage of the C-N bond of the intermediate G and simultaneous protonation. The mechanism of the ammonolysis of II is assumed to be similar to that proposed for the hydrolysis of the acetanilides.[19] The intermediate H would then dehydrate to the quinazoline derivative J. When X=Cl or Br, this in turn could readily undergo elimination of trihalomethyl group to give the 2(1H)-quinazolinone III. However, when R=H and X=F, loss of hydroxy ion to the 2-trifluoromethyl quinazoline IV would occur owing to the poor leaving ability of the trifluoromethyl group. The formation of the imine VIII is assumed to arise from the anion intermediate H by the initial cleavage of the C-N bond between positions 1 and 2 of the quinazoline ring and simultaneous proton transfer to the trihaloacetamide derivative K, probably followed by formation of the four-center intermediate L, which would readily eliminate trihaloacetate. Undoubtedly, kinetic studies are needed to prove the further detailed reaction mechanism.

Experimental

Melting points were determined in capillary tubes on a Thomas-Hoover melting point apparatus or a Ishii high melting point apparatus (air bath type) and are uncorrected. The latter was used for substances with melting points above 280°. The IR spectra were measured with a Hitachi EPI-G3 or Hitachi 285 spectrometer and the NMR spectra were recorded on a Varian T-60 instrument with tetramethyl silane (TMS) as internal standard. Thin-layer chromatography (TLC) was performed on silica gel with fluorescent indicator. The chromatograms were developed over a distance of 10 cm and then viewed under ultraviolet (UV) light. Anhydrous sodium sulfate was used for drying purposes unless otherwise stated.

Starting Materials——2-Aminophenyl ketones (I) were prepared by using the known procedures as follows. Most of the ketones were conveniently obtained from 2,3-disubstituted indoles by chromic acid oxidation or ozonolysis followed by alkaline or acidic hydrolysis.[7c,20] The rests of them were prepared *via* grignard reaction of 4H-3,1-benzoxazin-4-one,[21] Friedel-Crafts reaction of *p*-substituted aniline with aroyl chloride,[21a,22] by N-monoalkylation of the amino ketone,[7c] or by reduction of 2-acylaminophenyl ketone with lithium aluminum hydride, followed by oxidation of thus obtained N-substituted amino alcohol to the amino ketone.[23] The literature references are more specifically indicated in Table I.

2-Trihaloacetamidophenyl Ketones (II, Table I)——Several examples of the procedures for the synthesis of II are illustrated by the following.

5-Chloro-2-trichloroacetamidobenzophenone (II-4)——Method A: To a stirred solution of 23.2 g (100 mmol) of 2-amino-5-chlorobenzophenone in 200 ml of ether was added dropwise 20 g (110 mmol) of CCl_3COCl followed by 11 g (110 mmol) of triethylamine, the reaction temperature being kept at 5—15°. The resulting suspension was then stirred at room temperature for 3 hr and washed with water. The organic layer was dried and evaporated under reduced pressure. The residue was crystallized from EtOH to give 34.4 g (91%) of II-4 as colorless prisms, mp 91—92°. IR (Nujol mull): 3240 (amide NH), 1720 (amide C=O), 1640 cm^{-1} (C=O); NMR ($CDCl_3$) δ: 7.53—7.87 (m, 7H, aromatic), 8.65 (d, J=10 Hz, 1H, 3-H), 12.17 (s, 1H, NH).

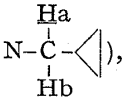
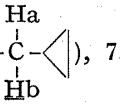
5-Chloro-2-tribromoacetamidobenzophenone (II-5)——Method B: To a stirred solution of 14.8 g (50 mmol) of CBr_3COOH in 100 ml of toluene was added 7.7 g (50 mmol) of $POCl_3$ followed by 11.6 g (50 mmol) of 2-amino-5-chlorobenzophenone. To the resulting suspension was added dropwise 10 g (100 mmol) of triethylamine below 15°, and the mixture was stirred at room temperature for 2 hr. The reaction mixture

19) V. Gani and P. Viout, *Tetrahedron Lett.*, **51**, 5241 (1972); A.M. Segretain, M. Beugelmans-Verrier, and M. Laloi-Diard, *Bull. Soc. Chim. Fr.*, **1972**, 3367.
20) *a*) Y. Sato, *Chem. Pharm. Bull.* (Tokyo), **11**, 1431 (1963); *b*) K. Schofield and R.S. Theobald, *J. Chem. Soc.*, **1950**, 1505; *c*) D.W. Ockenden and K. Schofield, *ibid.*, **1953**, 612.
21) *a*) L.H. Sternbach, R.I. Fryer, W. Metlesics, G. Sach, and A. Stempel, *J. Org. Chem.*, **27**, 3781 (1962); *b*) L. Berger, A. Stempel, L.H. Sternbach, E. Wenis, R.I. Fryer, and R.A. Schmidt, Belg. Patent 619, 101 [*Chem. Abstr.*, **59**, 10092 (1963)].
22) L.H. Sternbach, E. Reeder, O. Keller, and W. Metlesics, *J. Org. Chem.*, **26**, 4488 (1961).
23) F.H. McMillan and I. Pattison, Fr. Patent 1394287 [*Chem. Abstr.*, **63**, 8387 (1965)].

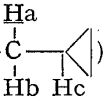
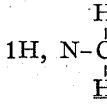
was diluted with 100 ml of EtOAc and worked up as described under method A. Recrystallization from iso-PrOH-1,2-dichloroethane gave 23.6 g (92%) of II-5 as light brown prisms, mp 113—115°. IR (Nujol mull): 3200 (amide NH), 1710 (amide C=O), 1640 cm^{-1} (C=O); NMR ($CDCl_3$) δ: 7.4—7.9 (m, 7H, aromatic), 8.59 (d, $J=10$ Hz, 1H, 3-H), 12.10 (s, 1H, NH).

5-Chloro-2-trifluoroacetamidobenzophenone (II-6)——Method C: To a stirred solution of 9.27 g (40 mmol) of 2-amino-5-chlorobenzophenone in 100 ml of ether was added dropwise 10.5 g (50 mmol) of $(CF_3CO)_2O$, the reaction temperature being kept at 5—15°. The resulting suspension was stirred at room temperature for 2 hr and the solvent was then evaporated under reduced pressure. The residual crystals were washed with water and recrystallized from EtOH to give 11.5 g (88%) of II-6 as colorless needles, mp 126—126.5°. IR (Nujol mull): 3250 (amide NH), 1730 (amide C=O), 1640 cm^{-1} (C=O); NMR ($CDCl_3$) δ: 7.53—7.90 (m, 7H, aromatic), 8.69 (d, $J=10$ Hz, 1H, 3-H), 11.97 (broad s, 1H, NH).

2-(N-Methyl-trichloroacetamido)-5-nitrobenzophenone (II-35)——Method D: A stirred mixture of 10.3 g (40 mmol) of 2-methylamino-5-nitrobenzophenone and 36.4 g (200 mmol) of CCl_3COCl was heated at 85° for 3 hr. The excess acid chloride was evaporated under reduced pressure and the residue was crystallized from EtOH to give 14.4 g (90%) of II-35 as colorless fine crystals, mp 120—121°. IR (Nujol mull): 1680 cm^{-1} (both C=O); NMR ($CDCl_3$) δ: 3.67 (s, 1H, NCH_3), 7.27—7.90 (m, 6H, aromatic), 8.33—8.55 (m, 2H, aromatic).

5-Chloro-2-(N-cyclopropylmethyl-trichloroacetamido)benzophenone (II-45)——Method E: To a solution of 14.3 g (50 mmol) of 5-chloro-2-cyclopropylmethylaminobenzophenone[7c] in 250 ml of ether was added dropwise 18.2 g (100 mmol) of CCl_3COCl followed by 10 g (100 mmol) of triethylamine. The stirred mixture was heated under reflux for 8 hr. After cooling, the reaction mixture was washed successively with water and dilute $NaHCO_3$ solution. The organic phase was dried and evaporated under reduced pressure. The residual oil was crystallized from EtOH to give 16.5 g (77%) of II-45 as colorless prisms, mp 101—102°. IR (Nujol mull): 1683 (amide C=O), 1670 cm^{-1} (C=O); NMR ($CDCl_3$) δ: 0—1.20 (m, 5H, cyclopropyl), 3.23 (m, 1H, ), 4.23 (m, 1H, ), 7.37—7.87 (m, 8H, aromatic).

From the mother liquor, after addition of hexane, an additional 2.4 g (11%) of II-45 was isolated.

5-Chloro-2-(N-cyclopropylmethyl-trifluoroacetamido)benzophenone (II-47)——Method F: To a solution of 6.55 g (20 mmol) of II-6 in 70 ml of DMF was added portionwise 1.0 g (22 mmol) of 50% NaH with ice-cooling, and the mixture was stirred at room temperature for 1 hr. To the mixture was added 5.4 g (36 mmol) of 90% cyclopropylmethyl bromide, and the resulting mixture was then heated at 100—110° for 10 hr. After cooling, the mixture was poured into 300 ml of ice-water and the resulting mixture was extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated. The residual oil was chromatographed on silica gel column using CH_2Cl_2 as eluent to give 5.37 g (70%) of II-47. Recrystallization from EtOH gave colorless prisms, mp 82.5—83.5°. IR (Nujol mull): 1695 (amide C=O), 1670 cm^{-1} (C=O); NMR ($CDCl_3$) δ: 0.07—1.33 (m, 5H, cyclopropyl), 3.13 (dd, $J_{ab}=14$ Hz, $J_{ac}=7$ Hz, 1H, ), 4.20 (dd, $J_{ab}=14$ Hz, $J_{bc}=7$ Hz, 1H, ), 7.4—7.9 (m, 8H, aromatic).

General Procedure for Reaction of 2-Trichloroacetamidobenzophenones with Ammonia in Various Conditions (Table II)——A mixture of 5 mmol of the 2-trichloroacetamidobenzophenone, at least twofold excess of NH_3 or an ammonium compound and a ten to fifteenfold amount of an appropriate solvent was allowed to react in various reaction conditions as summarized in Table II. The reaction was performed until the starting material (II) was gone or diminished to a considerably small extent as shown by TLC ($CHCl_3$ as developer). In case the solvent was other than DMSO and HMPT, the reaction mixture was concentrated under reduced pressure. In case DMSO or HMPT was used, the reaction mixture was poured into ice-water. The solid that formed was collected by filtration, washed with water, and then, if necessary with an appropriate organic solvent (*e.g.* ether, isopropyl ether, benzene, EtOAc, EtOH, CH_2Cl_2 or $CHCl_3$) to remove the contaminated benzophenone derivatives, and dried. In some cases that the yield of the product was comparatively low, the filtrate was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried, and evaporated. The residue was chromatographed on silica gel column using CH_2Cl_2 or $CHCl_3$ as an eluent.

The following examples are typical of the reaction procedures shown in Table II. These compounds are also listed in Table IV.

6-Chloro-4-phenyl-2(1H)-quinazolinone (III-4)——Method G. Experiment 1: To a solution of 3.77 g (10 mmol) of II-4 in 70 ml of MeOH was added 9 g (50 mmol) of a 10% (w/w) solution of NH_3 in MeOH. The mixture was stirred at room temperature for 24 hr, and then concentrated under reduced pressure in a water bath below 30°. The residue was triturated with a mixture of 50 ml of benzene and 50 ml of water. Insoluble material was then separated by filtration, washed successively with water and benzene, and dried to give

1.05 g (41%) of III-4. Recrystallization from DMF gave colorless plates, mp 321—323°, identical (TLC and IR) with a sample of III-4 prepared by the literature procedure.[7c] The benzene filtrate was separated, concentrated under reduced pressure, and absorbed on a silica gel column. Elution with $CHCl_3$ yielded 0.95 g (41%) of 2-amino-5-chlorobenzophenone as the first fraction and 0.28 g (7%) of unreacted II-4 as the second fraction.

Method H. Experiment 5: A mixture of 1.89 g (5 mmol) of II-4, 1.93 g (25 mmol) of $AcONH_4$, and 25 ml of DMSO was allowed to stir at room temperature for 24 hr. The solution was then poured into 150 g of ice-water. A precipitate formed was collected by filtration, washed with water, and dried to give 1.27 g (99%) of III-4 as colorless crystals showing only one spot on TLC (EtOAc as developer). The IR spectrum was identical with that of the product obtained according to method G.

6-Nitro-4-phenyl-2(1H)-quinazolinone (III-13)——Method I. Experiment 15: A mixture of 1.94 g (5 mmol) of II-15, 1.58 g (20 mmol) of NH_4HCO_3, and 25 ml of HMPT was heated at 100° for 4 hr. After cooling, the mixture was poured into 150 g of ice-water, and solids precipitated immediately. The precipitate was collected on a filter, washed with water, and dried to give 1.14 g (85%) of III-13. Recrystallization from DMF gave light brown fine crystals, mp 314—315°.

General Procedure for Reaction of 2-(N-Substituted trichloroacetamido)-5-chlorobenzophenone with Ammonium Acetate in Dioxane (Table III)——Method J: A mixture of 5 mmol of the 2-(N-substituted trichloroacetamido)-5-chlorobenzophenone, 1.93 g (25 mmol) of $AcONH_4$, and 20 ml of dioxane was stirred and heated at 90—95°. The progress of the reaction was followed by taking samples periodically and submitting them to TLC analysis. The solvent was evaporated under reduced pressure and the residue was partitioned between $CHCl_3$ and water. The $CHCl_3$ layer was washed with water, dried, concentrated to a small volume, and absorbed on a silica gel column. Elution with CH_2Cl_2 or $CHCl_3$ yielded the 2-aminobenzophenone (I) as a high *Rf* fraction, the starting material (II) as a medium *Rf* fraction, and the 2(1H)-quinazolinone as a final fraction.

2(1H)-Quinazolinones (III, Table IV) from 2-Trihaloacetamidobenzophenones (II)——Other methods employed for the preparation of 2(1H)-quinazolinones tabulated in Table IV are as follows.

Method H_1: A stirred mixture of 10 mmol of II, 20 mmol of $AcONH_4$, and 50 ml of DMSO was heated at 95—100° for 2 hr. After cooling, the reaction mixture was worked up as described under H.

Method H_2: The reaction was carried out at 75—80° as described under H_1.

Method H_3: The reaction was carried out at 55—60° for 3 hr as described under H_1.

Method H_4: A stirred mixture of 1.94 g (5 mmol) of II-16, 1.54 g (20 mmol) of $AcONH_4$, and 25 ml of DMSO was heated at 125° for 7 hr. The reaction mixture was then worked up as described under H.

Method J_1: A mixture of 5 mmol of II, 50 mmol of $AcONH_4$, and 25 ml of dioxane was stirred and refluxed for 16 hr.

Method J_2: The reaction was carried out as described under J. Dioxane was then removed under reduced pressure and the residue was triturated with isopropyl ether and water. Insoluble material was collected by filtration, washed with water and then with an appropriate organic solvent, and dried to give the crystalline product.

Method J_3: A mixture of 1.05 g (2.5 mmol) of II-38 1.54 g (20 mmol) of $AcONH_4$, and 15 ml of dioxane was heated in an autoclave at 130° (bath temperature) for 7 hr.

Method J_4: A mixture of 1.71 g (4 mmol) of II-48, 1.54 g (20 mmol) of $AcONH_4$, and 10 ml of dioxane was heated in an autoclave at 150° (bath temperature) for 8 hr.

8-Chloro-1-cyclopropylmethyl-4-phenyl-2(1H)-quinazolinone (III-41) and 3-Chloro-2-(N-cyclopropylmethyl-dichloroacetamidobenzophenone (XIa)[24]——Method K: A mixture of 1.29 g (3 mmol) of II-44, 1.39 g (18 mmol) of $AcONH_4$, and 10 ml of dioxane was stirred and heated at 95° for 5 hr. At that time TLC showed mostly starting material. After the addition of 0.93 g (12 mmol) of $AcONH_4$ and 10 ml of DMSO, the mixture was heated at 120° for 7 hr. To the mixture was again added 0.93 g (12 mmol) of $AcONH_4$, and heating was continued at 130° for additional 9 hr. After cooling, the reaction mixture was poured into ice-water. The resulting mixture was extracted with $CHCl_3$, and then worked up as described under method J to give 0.12 g (9%) of the starting material, 0.05 g (4%) of XIa as a light brown oil, and 0.34 g (37%) of III-41 as an amorphous solid. Compound III-41 was recrystallized from EtOH to give colorless scales, mp 163—164°. IR (Nujol mull): 1680, 1605, 1580, 1550 cm^{-1}; NMR ($CDCl_3$) δ: 0.40—0.63 (m, 4H, cyclopropyl CH_2), 1.13—1.60 (m, 1H, cyclopropyl CH), 4.87 (d, J=8 Hz, 2H, NCH_2), 7.17—7.92 (m, 8H, aromatic).

1-Cyclopropylmethyl-6-nitro-4-phenyl-2(1H)-quinazolinone (III-44)——Method L: A mixture of 1.77 g (4 mmol) of II-49, 3.1 g (40 mmol) of $AcONH_4$, and 25 ml of *t*-BuOH was heated under reflux for 8 hr. Isolation of the product in the same manner as described under method J afforded 0.10 g (8%) of 2-cyclopropylmethylamino-5-nitrobenzophenone and 1.12 g (87%) of III-44. The latter was recrystallized from EtOH to give light yellow needles, mp 172—173°. IR (Nujol mull): 1680, 1610, 1555, 1520 cm^{-1}; NMR ($CDCl_3$) δ: 0.53—0.70 (m, 4H, cyclopropyl CH_2), 1.02—1.55 (m, 1H, cyclopropyl CH), 4.35 (d, J=6 Hz, 2H, NCH_2),

24) This compound was identical with that obtained under method D. See Table I, footnote *p*.

7.53—7.85 (m, 6H, aromatic), 8.53 (dd, $J_{5,7}=3$ Hz, $J_{7,8}=10$ Hz, 1H, 7-H), 8.73 (d, $J_{5,7}=3$ Hz, 1H, 5-H).

6-Chloro-1-cyclopropylmethyl-4-phenyl-2(1H)-quinazolinone (III-42) and 5-Chloro-2-cyclopropylmethylaminobenzophenone Imine (VIIIb)——A. Method M: A mixture of 1.29 g (3 mmol) of II-45 and 5 ml of liquid NH_3 in an autoclave was kept at room temperature for 20 hr. After NH_3 was evaporated at room temperature, the residue was dissolved in CH_2Cl_2. Insoluble material was then separated by filtration and the filtrate was evaporated. The residue was chromatographed on activated neutral alumina using CH_2Cl_2 as an eluent to give 0.43 g (50%) of VIIIb as a yellow oil and 0.46 g (49%) of III-42 as pale yellow crystals, mp 172—173°. A sample of the oily VIIIb was submitted for analysis. IR (neat): 3270—2840, 1600, 1580, 1560, 1505 cm^{-1}; NMR (CCl_4) δ: 0.23—0.60 (m, 4H, cyclopropyl CH_2), 1.1 (m, 1H, cyclopropyl CH), 3.07 (d, $J=7$ Hz, 2H, NCH_2), 4.7 (s, 1H, imine NH), 6.6 (d, $J_{3,4}=9$ Hz, 1H, 3-H), 6.93 (d, $J_{4,6}=2$ Hz, 1H, 6-H), 7.1 (dd, $J_{3,4}=9$ Hz, $J_{4,6}=2$ Hz, 1H, 4-H), 7.37 (s, 5H, aromatic), 9.4 (broad s, 1H, NH). *Anal.* Calcd. for $C_{17}H_{17}ClN_2$: C, 71.70; H, 6.02; Cl, 12.45; N, 9.84. Found: C, 71.34; H, 6.08; Cl, 12.63; N, 9.97.

B. Reaction under Method H: A mixture of 2.16 g (5 mmol) of II-45 and 1.93 g (25 mmol) of $AcONH_4$ in 30 ml of DMSO was stirred at room temperature for 6 hr. The reaction mixture was poured into ice-water and resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with dilute $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, and concentrated to dryness. The oily residue was chromatographed on activated neutral alumina using CH_2Cl_2 as an eluent to give 0.50 g (32%) of III-42 as pale yellow crystals and 1.0 g (*ca.* 67%) of VIIIb as a yellow oil containing small quantity of 5-chloro-2-cyclopropylmethylaminobenzophenone (Ib) as shown by TLC ($CHCl_3$ as developer).

6-Chloro-1-methyl-4-phenyl-2(1H)-quinazolinone (III-32) and 5-Chloro-2-methylaminobenzophenone Imine (VIIIa)——A mixture of 1.17 g (3 mmol) of II-34 and 1.16 g (15 mmol) of $AcONH_4$ in 20 ml of DMSO was allowed to react at room temperature and worked up as described above to give 0.77 g of the oily product consisting of a mixture of 5-chloro-2-methylaminobenzophenone (Ia), VIIIa and III-32 as shown by TLC ($CHCl_3$ as developer). The mixture was chromatographed on activated neutral alumina using benzene as an eluent. The first material off of the column was not the imine VIIIa but the benzophenone Ia (62%) and the second material was III-32 (36%).

Reaction of II-34 with Ammonia in Methanol (Table II, Experiment 17)——To a solution of 3.91 g (10 mmol) of II-34 in 150 ml of MeOH was added 35 g (200 mmol) of a 10% (w/w) solution of NH_3, and the mixture was allowed to stand at room temperature for 3 days. The resulting mixture was concentrated under reduced pressure and the residue was triturated with ether. Insoluble material was collected by filtration, washed successively with ether and water, and dried to give 2.14 g (71%) of 6-chloro-1,4-dihydro-4-methoxy-1-methyl-4-phenyl-2H-3,1-benzoxazin-2-one (VIa). Recrystallization from EtOH gave colorless scales, mp 156—157°. IR (Nujol mull): 1743, 1720, 1605, 1590, 1500 cm^{-1}; NMR ($CDCl_3$) δ: 3.37 (s, 3H, NCH_3 or OCH_3), 3.42 (s, 3H, OCH_3 or NCH_3), 6.91 (d, $J=8$ Hz, 1H, 8-H), 7.0 (d, $J=2$ Hz, 1H, 5-H), 7.33 (dd, $J_{5,7}=2$ Hz, $J_{7,8}=8$ Hz, 1H, 7-H), 7.45 (s, 5H, aromatic); MS *m/e*: 303 (M^+), 272 (M^+-OCH_3), 259 (M^+-CO_2). *Anal.* Calcd. for $C_{16}H_{14}ClNO_3$: C, 63.27; H, 4.65; Cl, 11.67; N, 4.61. Found: C, 63.00; H, 4.66; Cl, 11.63; N, 4.56.

The filtrate was concentrated and the residue was separated on 20×20 cm silica gel thick layer plates using benzene–EtOAc (5: 2) as an eluent to give 0.13 g (5%) of Ia, 0.12 g (4%) of VIa, 0.21 g (7%) of 5-chloro-2-(N-methyl-methoxycarbonylamino)benzophenone (VIIa), and 0.16 g (6%) of III-32. Compound VIIa was crystallized from isopropyl ether to give colorless prisms, mp 89—90°. IR (Nujol mull): 1700 (ester C=O), 1670 (C=O), 1600, 1565 cm^{-1}; NMR ($CDCl_3$) δ: 3.17 (s, 3H, NCH_3 or OCH_3), 3.43 (s, 3H, OCH_3 or NCH_3), 7.37—7.93 (m, 8H, aromatic). *Anal.* Calcd. for $C_{16}H_{14}ClNO_3$: C, 63.27; H, 4.65; Cl, 11.67; N, 4.61. Found: C, 63.54; H, 4.63; Cl, 11.77; N, 4.43.

4-Benzylidene-1,4-dihydro-1,6-dimethyl-2H-3,1-benzoxazin-2-one (IX)——To a solution of 3.85 g (10 mmol) of benzyl 5-methyl-2-(N-methyl-trichloroacetamido)phenyl ketone (II-36) in 50 ml of EtOH was added 3.85 g (50 mmol) of $AcONH_4$. The mixture was refluxed with stirring for 12 hr and then worked up as described under method J. Chromatography of the residue on silica gel using chloroform yielded 0.79 g (33%) of benzyl 5-methyl-2-methylaminophenyl ketone as the first fraction and 0.97 g (37%) of IX as the second fraction. Compound IX was recrystallized from MeOH–petroleum benzine to give colorless needles, mp 132—133°. IR (Nujol mull): 1735, 1720 (O–CO–N), 1640 cm^{-1} (C=C); NMR ($CDCl_3$) δ: 2.33 (s, 3H, CH_3), 3.37 (s, 3H, NCH_3), 6.13 (s, 1H, CH), 6.70—7.83 (m, 8H, aromatic). *Anal.* Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.18; H, 5.50; N, 5.07.

Reaction of II-5 with Ammonia in Ethanol——To a solution of 1.53 g (3 mmol) of II-5 in 80 ml of EtOH was added 5.1 g (30 mmol) of a 10% (w/w) solution of NH_3 in EtOH. The mixture was then heated in an autoclave at 90—95° (bath temperature) for 6 hr. After the solvent was evaporated, the residue was triturated with CH_2Cl_2. Insoluble material was collected by filtration, washed successively with CH_2Cl_2 and water, and dried to give 0.24 g (31%) of III-4. TLC (EtOAc) showed only one spot. The filtrate was worked up as usual to be chromatographed on a silica gel column. Elution with $CHCl_3$ yielded 0.39 g of crude products as the first fraction, 0.21 g (23%) of (2-benzoyl-4-chlorophenyl)oxamide (X) as the second fraction. Further elution with EtOAc yielded 0.04 g (5%) of III-4 as a final fraction. Compound X was recrystallized from

a mixture of DMF and $CHCl_3$ to give colorless plates, mp 210.5—211° (lit.[25] mp 209—210°). IR (Nujol mull): 3400, 3290, 3210, 1680, 1650, 1600, 1580, 1520 cm^{-1}. *Anal.* Calcd. for $C_{15}H_{11}ClN_2O_3$: C, 59.52; H, 3.66; Cl, 11.71; N, 9.25. Found: C, 59.33; H, 3.48; Cl, 12.00; N, 9.34.

The first fraction above obtained was separated on 20×20 cm silica gel thick layer plates using benzene as developer to give 0.02 g (1.3%) of the starting material as a high *Rf* band, 0.18 g (14%) of 5-chloro-2-dibromoacetamidobenzophenone (XId) as a medium *Rf* band, and 0.12 g (13%) of 5-chloro-2-ethoxycarbonylaminobenzophenone (VIIc) as a low *Rf* band.

Compound XId was recrystallized from iso-PrOH to give pale yellow needles, mp 106—107°. IR (Nujol mull): 3200 (amide NH), 1695 (amide C=O), 1635 (C=O), 1598, 1580, 1515 cm^{-1}. *Anal.* Calcd. for $C_{15}H_{10}Br_2ClNO_2$: C, 41.75; H, 2.34; Br, 37.03; Cl, 8.22; N, 3.25. Found: C, 41.60; H, 2.21; Br, 37.23; Cl, 7.89; N, 3.22.

Compound VIIc was recrystallized from iso-PrOH to give pale yellow needles, mp 75—76° (lit.[26] mp 80—82°). The IR spectrum was identical with that of an authentic sample.

Reaction of 2-Trifluoroacetamidobenzophenones with Ammonia——A. 6-Chloro-4-phenyl-2-trifluoromethylquinazoline (IVa): The reaction of 3.28 g (10 mmol) of II-6 with 1.54 g (20 mmol) of $AcONH_4$ in 30 ml of DMSO was carried out as described under method H_1. The precipitate was collected, washed with water and dried to give 2.96 g (96%) of IVa. Recrystallization from EtOH gave pale yellow needles, mp 123—124°. IR (Nujol mull): 1600, 1560, 1540, 1500 cm^{-1}. *Anal.* Calcd. for $C_{15}H_8ClF_3N_2$: C, 58.37; H, 2.61; Cl, 11.48; N, 9.07. Found: C, 58.36; H, 2.66; Cl, 11.37; N, 9.02.

The reaction of II-6 with ammonia under the same conditions as described in method G afforded only 2-amino-5-chlorobenzophenone.

B. 6-Methyl-2-pentafluoroethyl-4-phenylquinazoline (IVb): 2-Amino-5-methylbenzophenone (6.34 g) was acylated as described in method B with 4.92 g of perfluoropropionic acid. The crude product was crystallized from isopropyl ether to give 8.22 g (77%) of 5-methyl-2-perfluoropropionamidobenzophenone. Recrystallization from iso-PrOH–H_2O gave pale yellow needles, mp 74—75°. IR (Nujol mull): 3080 (amide NH), 1730 (amide C=O), 1640 (C=O), 1595, 1525 cm^{-1}. *Anal.* Calcd. for $C_{17}H_{12}F_5NO_2$: C, 57.15; H, 3.39; N, 3.92. Found: C, 57.23; H, 3.21; N, 3.80.

The reaction of 0.72 g (2 mmol) of the perfluoropropionamidobenzophenone with 0.32 g (4 mmol) of $AcONH_4$ in the same manner as described above in A afforded 0.65 g (96%) of IVb. Recrystallization from EtOH gave colorless needles, mp 112—113°. IR (Nujol mull): 1600, 1565, 1540, 1500 cm^{-1}; NMR ($CDCl_3$) δ: 2.6 (s, 3H, CH_3), 7.5—8.2 (m, 8H, aromatic). *Anal.* Calcd. for $C_{17}H_{11}F_5N_2$: C, 60.36; H, 3.28; N, 8.28. Found: C, 60.58; H, 3.21; N, 8.18.

C. Ib and III-42 from II-47: The reaction of 0.95 g (2.5 mmol) of II-47 with 0.39 g (5 mmol) of $AcONH_4$ was carried out as described under method H_1 with the following changes: the mixture was heated for 10 hr, the product was extracted with EtOAc, after removal of the solvent the residue was chromatographed on silica gel using CH_2Cl_2 as an eluent. The first fraction yielded 0.50 g (70%) of Ib and the second fraction yielded 0.01 g (13%) of III-42.

The reaction of II-47 with $AcONH_4$ in the same manner as described under method J afforded only a trace of Ib as shown by TLC.

Ethyl 2-Trichloroacetamidobenzoate (XII)——To a solution of 8.26 g (50 mmol) of ethyl 2-aminobenzoate in 100 ml of ether was added 9.1 g (50 mmol) of CCl_3COCl, and the mixture was stirred at room temperature for 5 hr. After addition of 100 ml of ether, the resulting mixture was washed with water. The organic phase was then washed with dilute $NaHCO_3$ solution, dried and concentrated to dryness to give 14.8 g (95%) of XII as a white solid. Recrystallization from EtOH–*n*-hexane gave colorless needles, mp 92.5—93.5°. IR (Nujol mull): 3100, 1720, 1700, 1610, 1595, 1550, 1540, 1515 cm^{-1}; NMR ($CDCl_3$) δ: 1.4 (t, J=7 Hz, 3H, $CH_2\underline{CH_3}$), 4.4 (q, J=7 Hz, 2H, $\underline{CH_2}CH_3$), 7.03—7.73 (m, 2H, 4-H and 5-H), 8.1 (dd, $J_{5,6}$=8 Hz, $J_{4,6}$=2 Hz, 1H, 6-H), 8.67 (dd, $J_{3,4}$=8 Hz, $J_{3,5}$=2 Hz, 1H, 3-H), 12.47 (broad s, 1H, NH). *Anal.* Calcd. for $C_{11}H_{10}Cl_3NO_3$: C, 42.54; H, 3.25; Cl, 34.25; N, 4.51. Found: C, 42.30; H, 3.15; Cl, 34.51; N, 4.51.

2,4(1H, 3H)-quinazolinedione (XIII)——A mixture of 1.55 g (5 mmol) of XII, 1.54 g (20 mmol) of $AcONH_4$ and 25 ml of DMSO was stirred at room temperature for 24 hr. At that time TLC [benzene–EtOAc (5: 2) as developer] showed that most of the starting material remained. Accordingly 1.54 g more of $AcONH_4$ was added and the resulting mixture was then heated to 90—95° for 4 hr with stirring. After cooling, the mixture was poured into ice-water, and the resulting solid was collected by filtration, washed with water, and dried to give 0.63 g (78%) of XIII as a light brown solid. Recrystallization from DMF–$CHCl_3$ gave colorless prisms, mp 358° (lit.[27] mp 351—352°). *Anal.* Calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.27. Found: C, 59.27; H, 3.81; N, 17.27.

25) H. Zenno, T. Kamiya, and H. Yazawa, Japan Patent 19587 (1967) [*Chem. Abstr.* **69**, 1885l*n* (1968)]; K. Ishizumi, S. Inaba, and H. Yamamoto, *J. Org. Chem.*, **39**, 2587 (1974).
26) E. Testa, L. Fontanella, and M. Bovara, *Farmaco Ed. Sci.*, **18**, 815 (1963) [*Chem. Abstr.*, **60**, 6848*d* (1964)].
27) G. Doleschall and K. Lempert, *Monatsh. Chem.*, **95**, 1068 (1964).

2-Trichloroacetamidobenzonitrile (XIV)——Anthranilonitrile (11.8 g, 100 mmol) was trichloroacetylated and worked up as described under method A. Recrystallization from isopropyl ether gave 20.3 g (77%) of XIV as colorless needles, mp 94—95°. IR (Nujol mull): 3300, 2230, 1730, 1720, 1600, 1510, 1495 cm^{-1}; NMR ($CDCl_3$) δ: 7.17—7.80 (m, 3H, aromatic), 8.37 (dd, $J_{3,4}=8$ Hz, $J_{3,5}=2$ Hz, 1H, 3-H), 8.97 (broad s, 1H, NH). *Anal.* Calcd. for $C_9H_5Cl_3N_2O$: C, 41.02; H, 1.91; Cl, 40.36; N, 10.63. Found: C, 41.27; H, 2.05; Cl, 40.12; N, 10.59.

4-Amino-2(1H)-quinazolinone (XV)——A mixture of 1.32 g (5 mmol) of XIV, 2.31 g (30 mmol) of $AcONH_4$ and 25 ml of DMSO was stirred at room temperature for 20 hr. At that time TLC [benzene-AcOEt (5: 2) as developer] showed only a starting material, so the mixture was then heated to 90—95° for 8 hr. After cooling, the mixture was poured into ice-water, basified with Na_2CO_3. The precipitate formed was filtered, washed with water, and dried to give 0.44 g (55%) of XV as a white amorphous solid. Recrystallization from DMF–EtOH gave colorless needles, mp>360° (lit.[28] mp>350°). *Anal.* Calcd. for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.23; H, 4.52; N, 25.75.

4-Chlorophenylurea (XVIIa)——A. With Ammonium Acetate in DMSO: A mixture of 1.37 g (5 mmol) of 2,2,2,4′-tetrachloroacetanilide (XVIa),[29] 3.1 g (40 mmol) of $AcONH_4$ and 25 ml of DMSO was heated at 100° for 4 hr. The work-up as described in method H gave 0.43 g (50%) of XVIIa, which was recrystallized from DMF–$CHCl_3$ for analysis, mp 213—213.5° (lit.[30] mp 212°). *Anal.* Calcd. for $C_7H_7ClN_2O$: C, 49.28; H, 4.14; Cl, 20.78; N, 16.42. Found: C, 49.20; H, 4.16; Cl, 20.96; N, 16.20.

The mother liquor was neutralized with $NaHCO_3$, extracted with benzene, and washed with water. The extract was dried and evaporated to yield 0.16 g (25%) of crude *p*-chloroaniline.

B. With Liquid Ammonia: The reaction of 1.37 g (5 mmol) of XVIa with 7 ml of liquid NH_3 was carried out as described under method M. The residue was triturated with water, filtered, washed with water, and dried to give 0.80 g (94%) of XVIIa, mp 208°.

N-Cyclopropylmethyl-4-chloroaniline——To a solution of 6.38 g (50 mmol) of 4-chloroaniline in 50 ml of DMF was added portionwise 2.4 g (50 mmol) of 50% NaH, and the mixture was stirred at room temperature for 1 hr. To the mixture was then added 9.0 g (60 mmol) of 90% cyclopropylmethyl bromide. The resulting mixture was further stirred at room temperature for 24 hr and then poured into ice-water. The mixture was extracted with benzene and worked up as usual. The residue was chromatographed on silica gel column using benzene as an eluent to give 4.65 g (51%) of N-cyclopropylmethyl-4-chloroaniline as colorless oil. IR (neat): 3420 (NH), 3080—2840, 1600, 1500 cm^{-1}; NMR (CCl_4) δ: 0—1.3 (m, 5H, cyclopropyl), 2.9 (d, $J=7$ Hz, 2H, NCH_2), 3.63 (s, 1H, NH), 6.4 (d, 2H, aromatic), 7.07 (d, 2H, aromatic). *Anal.* Calcd. for $C_{10}H_{12}ClN$: C, 66.11; H, 6.66; Cl, 19.51; N, 7.71. Found: C, 66.20; H, 6.53; Cl, 19.43; N, 7.44.

N-Cyclopropylmethyl-2,2,2,4′-tetrachloroacetanilide (XVIb)——N-Cyclopropylmethyl-4-chloroaniline (4.18 g, 23 mmol) in 50 ml of benzene was trichloroacetylated and worked up as described under method A. Chromatography of the residue on silica gel using benzene as an eluent gave 7.22 g (96%) of XVIb as light brown oil, which was solidified by storing in a refrigerator. Recrystallization from *n*-hexane–EtOH gave colorless prisms, mp 53—54°. IR (Nujol mull): 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ: 0—1.27 (m, 5H, cyclopropyl), 3.7 (d, $J=7$ Hz, 2H, NCH_2), 7.37 (s, 4H, aromatic). *Anal.* Calcd. for $C_{12}H_{11}Cl_4NO$: C, 44.07; H, 3.39; Cl, 43.36; N, 4.28. Found: C, 43.84; H, 3.30; Cl, 43.34; N, 4.24.

N-Cyclopropylmethyl-N-(4-chlorophenyl)urea (XVIIb)——The reaction of 0.98 g (3 mmol) of XVIb with 5 ml of liquid NH_3 was carried out as described under method M. The residue was partitioned between $CHCl_3$ and water. $CHCl_3$ layer was then washed with water, dried and evaporated to give 0.67 g (100%) of XVIIb as colorless crystals. Recrystallization from EtOH–*n*-hexane gave colorless needles, mp 115—116°. IR (Nujol mull): 3430, 3200 (NH), 1650 (amide C=O), 1610, 1595, 1495 cm^{-1}; NMR ($CDCl_3$) δ: 0—1.20 (m, 5H, cyclopropyl), 3.50 (d, 2H, NCH_2), 4.83 (broad s, 2H, NH_2), 7.20—7.53 (m, 4H, aromatic). *Anal.* Calcd. for $C_{11}H_{13}ClN_2O$: C, 58.80; H, 5.83; Cl, 15.78; N, 12.47. Found: C, 58.73; H, 5.72; Cl, 15.93; N, 12.36.

The IR spectrum of this material was identical with that obtained by reaction of N-cyclopropylmethyl-4-chloroaniline with KCNO.

Acknowledgement The authors wish to thank Mr. M. Koshiba for his skillful technical assistance and the members of the Analytical Section of this company for the microanalyses.

28) K.W. Breukink and P.E. Verkade, *Rec. Trav. Chim.*, **79**, 443 (1960).
29) N.G. Clark and A.F. Hams, *Biochem. J.*, **55**, 839 (1953).
30) G.R. Elliott, *J. Chem. Soc.*, **123**, 804 (1923).