with 2-methylamino-5-chlorobenzophenone and 2-amino-5-chlorobenzophenone. The infrared spectrum confirmed the absence of an NH grouping.

Acknowledgment.—We are indebted to Dr. A. Motchane and Mr. S. Traiman for the infrared spectra, to Dr. Al Steyermark and his staff for microanalyses, and to Mrs. B. Sluboski for the compilation of the tables. Mr. L. A. Dolan was helpful in the preparation of larger amounts of starting materials and intermediates.

Quinazolines and 1,4-Benzodiazepines. VI.[1a] Halo-, Methyl-, and Methoxy-substituted 1,3-Dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones[1b,c]

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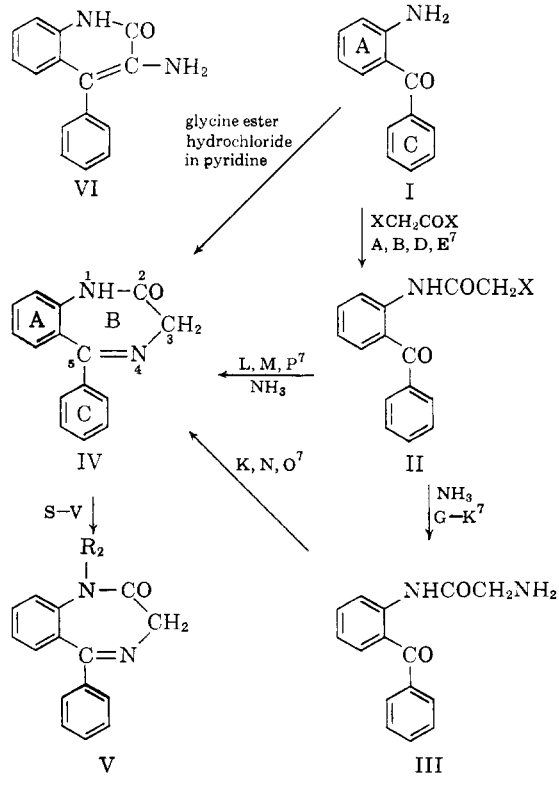
Two new methods for the synthesis of 1,4-benzodiazepin-2-ones are reported. A number of new 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones, and intermediates leading to these compounds, are described.

In view of the interesting psychopharmacological properties[2] of the 1,4-benzodiazepin-2-ones described in a previous paper,[3] a series of related compounds was synthesized. This paper describes the preparation of 1,4-benzodiazepin-2-ones (IV) with halogens, methyl or methoxyl groups in different positions in rings A and C, and the synthesis of derivatives bearing substituents in ring B (positions 1 and 3).

Since the synthetic approaches, previously reported,[3] did not lend themselves to the preparation of a larger variety of compounds, alternative routes were studied which led to two new syntheses of benzodiazepin-2-ones IV.[4]

The first series of reactions consisted of three steps. The haloacetamido compounds II, (Table I) were prepared in the customary way from aminobenzophenones (I),[5] bearing the desired substituents in rings A and C.

Ammonolysis of these compounds in liquid ammonia gave the aminoacetamido derivatives (III)[6] (Table II) which were cyclized to the benzodiazepinones (IV) (Table III) in some cases by direct fusion, or preferably by refluxing in a solvent, such as ethanol, benzene, or pyridine. Refluxing a dilute pyridine solution generally gave the best results. The cyclization gave over-all yields of about 30–



(1) (a) Paper V, L. H. Sternbach, R. Ian Fryer, W. Metlesics, G. Sach, and A. Stempel, *J. Org. Chem.*, **27**, 3781 (1962). (b) The nomenclature for the 1,4-benzodiazepinones was adopted after consultation with Dr. L. T. Capell of *Chem. Abstr.* (c) After the manuscript had been prepared a paper was published by S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *J. Org. Chem.*, **27**, 562 (1962), which contains a few of the compounds described in this paper.

(2) L. O. Randall, G. A. Heise, W. Schallek, R. E. Bagdon, R. Banziger, A. Boris, R. A. Moe, and W. Abrams, *Current Therapeutic Research*, **3**, 405 (1961); L. O. Randall and B. Kappell, *Biochem. Pharm.*, **6**, 16 (1961); L. O. Randall, Sixth Hahnemann Symposium, Psychosomatic Medicine, in press.

(3) Paper IV of this series. L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).

(4) These compounds and the intermediates leading to them (II and III) are shown in the tables. The same Arabic numerals were assigned to compounds bearing the same substituents in rings A and C. Additional Arabic numerals are given to benzodiazepinones with substituents in ring B, but in the latter case related compounds also bear the same Arabic numerals (for example II-4 and IV-4). Substituents R_2–R_9 have the same meaning as in the preceding paper (No. V).[1a]

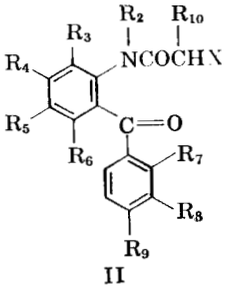
(5) Literature references for *o*-aminobenzophenones: I-1, F. Ullmann and H. Bleier, *Ber.*, **35**, 4273 (1902). I-17, J. F. J. Dippy and V. Moss *J. Chem. Soc.*, 2205 (1952). I-37, P. Kränzlein, *Ber.*, **70**, 1784 (1937). I-20, 21, 22, 23, 33, 38, 40, 42, Paper III, L. H. Sternbach, E. Reeder, O. Keller, and W. Metlesics, *J. Org. Chem.*, **26**, 4488 (1961). I-14, 15, 18, 27, 28, 29, 30, 31, 34, 35, 41, 43, 44, 49, and acetyl derivatives of 45 and 47, see paper V. I-48 was prepared according to Lothrop and Goodwin (Paper V) and converted without purification into II-48.

(6) It is interesting to note that the infrared absorption spectra of these compounds in 3% chloroform solution were hardly distinguishable from those of the starting materials II. Both show two carbonyl bands of medium strength at about 1690 cm.$^{-1}$ and 1650 cm.$^{-1}$. The primary amino group of III causes only a barely noticeable shoulder at 3400 cm.$^{-1}$.

(7) The letters indicate the methods described in the Experimental.

TABLE I

2-HALOACETAMIDOBENZOPHENONES



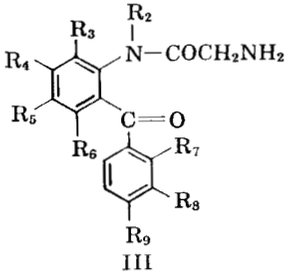
II

	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	X	Method[a]	Cryst. from[b]	M.p., °C.	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	H	H	H	H	H	H	H	H	H	Br	A	m.	94–95	86	$C_{15}H_{12}BrNO_2$	56.80	3.50	56.90	3.71
3-Cl	H	H	H	Cl	H	H	H	H	H	Cl	B	b. + p.	117–118	85	$C_{15}H_{11}Cl_2NO_2$	58.46	3.60	58.58	4.01
3-Br	H	H	H	Cl	H	H	H	H	H	Br	A	$CHCl_3$ + h.	124–125	89	$C_{15}H_{11}BrClNO_2$	51.09	3.14	50.94	3.00
4-Cl	CH_3	H	H	Cl	H	H	H	H	H	Cl	A	m.	123–124	95	$C_{16}H_{13}Cl_2NO_2$	59.64	4.06	59.53	3.85
4-Br	CH_3	H	H	Cl	H	H	H	H	H	Br	A	e.	95–96	84	$C_{16}H_{13}BrClNO_2$	52.41	3.57	51.98	3.64
4-I	CH_3	H	H	Cl	H	H	H	H	H	I	C	e.	95	85	$C_{16}H_{13}ClINO_2$	46.46	3.17	46.59	3.35
5	C_6H_5—CH_2	H	H	Cl	H	H	H	H	H	Br	A	$CHCl_3$ + h.	159–160	78	$C_{22}H_{17}BrClNO_2$	59.68	3.87	59.84	4.23
6	CH_2=CH—CH_2	H	H	Cl	H	H	H	H	H	Br	A	h.	85–86	85	$C_{18}H_{15}BrClNO_2$	55.05	3.87	54.82	3.93
7	H	H	H	Cl	H	H	H	H	CH_3	Br	B	e. + p.	114–115	30	$C_{16}H_{13}BrClNO_2$	52.41	3.57	52.37	3.87
15	H	H	H	H	Cl	H	H	H	H	Br	B[c]		97–98	59	$C_{15}H_{11}BrClNO_2$	51.09	3.14	51.16	3.16
16	H	Cl	H	H	H	H	H	H	H	Br	D	b. + h.	129–130	70	$C_{15}H_{11}BrClNO_2$	51.09	3.14	51.25	3.64
17	H	H	H	F	H	H	H	H	H	Br	A	e.	103–105	93	$C_{15}H_{11}BrFNO_2$	53.59	3.30	53.12	3.67
18	H	H	H	H	H	F	H	H	H	Br	A	m.	117–118	74.5	$C_{15}H_{11}BrFNO_2$	53.59	3.30	53.47	3.59
20	H	H	H	Br	H	H	H	H	H	Br	D	m.	117–118	91	$C_{15}H_{11}BrNO_2$	45.37	2.79	44.94	2.84
21	H	Cl	H	Cl	H	H	H	H	H	Br	A	m.	162–163	66	$C_{15}H_{10}BrCl_2NO_2$	46.54	2.60	46.99	2.68
22	H	H	H	Cl	H	H	H	Cl	H	Br	A	b. + e.	127–128	68	$C_{15}H_{10}BrCl_2NO_2$	46.54	2.60	46.76	2.68
23-Cl	H	H	H	Cl	H	Cl	H	H	H	Cl	A	m.	157–159	88	$C_{15}H_{10}Cl_3NO_2$	52.58	2.94	52.61	3.21
23-Br	H	H	H	Cl	H	Cl	H	H	H	Br	A	b. + h.	133–135	90	$C_{15}H_{10}BrCl_2NO_2$	46.54	2.60	46.81	2.77
27-Cl	H	H	H	Cl	H	F	H	H	H	Cl	A	e.	141–142	90	$C_{15}H_{10}Cl_2FNO_2$	55.24	3.09	55.34	3.16
27-Br	H	H	H	Cl	H	F	H	H	H	Br	A	m.	132–133	97	$C_{15}H_{10}BrClFNO_2$	48.61	2.72	48.80	2.72
30	H	H	H	Cl	H	H	H	F	H	Br	A	e.	97–98	25.8	$C_{15}H_{10}BrClFNO_2$	48.61	2.72	48.74	2.75
31	H	H	H	Br	H	F	H	H	H	Br	A	m.	139–140	80	$C_{15}H_{10}Br_2FNO_2$	43.40	2.43	43.53	2.51
35	H	H	H	Cl	H	CH_3	H	H	H	Br	E	b.	137–138	83	$C_{16}H_{13}BrClNO_2$	52.41	3.57	52.54	3.87
38	H	H	H	CH_3	H	H	H	H	H	Br	A	b. + p.	116–117	87	$C_{16}H_{14}BrNO_2$	57.85	4.25	57.62	4.48
42	H	H	OCH_3	H	H	H	H	H	H	Br	F	b. + h.	107–108	69	$C_{16}H_{14}BrNO_3$	55.19	4.05	55.54	3.99
44	H	H	OCH_3	Br	H	H	H	H	H	Br	A	b. + h.	144–145	75	$C_{16}H_{13}Br_2NO_3$	44.99	3.07	45.35	3.10
45	H	H	H	Cl	H	OCH_3	H	H	H	Br	F	CH_3CN	129–130	53	$C_{16}H_{13}BrClNO_3$	50.22	3.42	49.85	3.50
47	H	H	H	Cl	H	H	H	OCH_3	H	Br	F	b. + h.	116–118	71	$C_{16}H_{13}BrClNO_3$	50.22	3.42	50.44	3.76
48	H	H	H	Cl	H	H	OCH_3	H	H	Br	F	h.	97–98	60	$C_{16}H_{13}BrClNO_3$	50.22	3.42	49.86	3.62

[a] Methods A, B, D, and E could probably be interchanged in most cases. [b] m. = methanol, p. = petroleum ether, b.p. 30–60°, b. = benzene, e. = ether, h. = hexane. All compounds formed colorless prisms or needles. [c] Ether was used instead of dioxane in the reaction. The extraction was done with ether.

TABLE II

2-AMINOACETAMIDOBENZOPHENONES



III

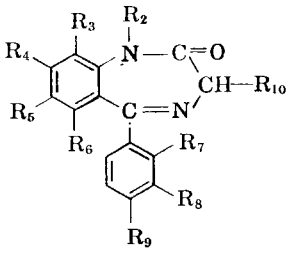
	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	Method	Cryst. from[a]	M.p., °C.	Yield, %	Formula	—Calcd., %— C	H	—Found, %— C	H
3	H	H	H	Cl	H	H	H	H	G	b. + h.	97–99	93	$C_{15}H_{13}ClN_2O_2$	62.40	4.54	62.26	4.78
3·HCl	H	H	H	Cl	H	H	H	H	J	m. + e.	192–193 dec.	90.2	$C_{15}H_{13}ClN_2O_2$·HCl	55.55	4.34	55.51	4.63
15	H	H	H	H	Cl	H	H	H	L[b]	b. + h.	73–75	25	$C_{15}H_{13}ClN_2O_2$	62.40	4.54	62.74	4.65
17·HCl	H	H	H	F	H	H	H	H	G + J[c]	m. + e.	242–243	80	$C_{15}H_{13}FN_2O_2$·HCl	58.35	4.57	58.71	5.08
22	H	H	H	Cl	H	H	H	Cl	G	CH_2Cl_2, + p.	139–140	79	$C_{15}H_{12}Cl_2N_2O_2$	55.75	3.74	55.85	3.58
23	H	H	H	Cl	H	Cl	H	H	H	e.	122–124	85	$C_{15}H_{12}Cl_2N_2O_2$	55.75	3.74	56.16	3.77
27	H	H	H	Cl	H	F	H	H	G	b. + h.	115–115.5	78	$C_{15}H_{12}ClFN_2O_2$	58.74	3.94	58.43	4.06
31	H	H	H	Br	H	F	H	H	G	b. + h.	110–111	87	$C_{15}H_{12}BrFN_2O_2$	51.30	3.44	50.75	3.58
31·HCl	H	H	H	Br	H	F	H	H	J	m. + e.	184–185	95	$C_{15}H_{12}BrFN_2O_2$·HCl	46.48	3.38	46.43	3.25
35	H	H	H	Cl	H	CH_3	H	H	H	CH_2Cl_2, h.	121–123	33[d]	$C_{16}H_{15}ClN_2O_2$	63.47	4.99	63.39	5.16
44	H	H	OCH_3	Br	H	H	H	H	K	b.	161–163	30	$C_{16}H_{15}BrN_2O_3$	52.90	4.16	52.96	4.45

[a] b. = benzene, h. = hexane, m. = methanol, e. = ether, p. = petroleum ether, b.p. 30–60°. The products formed colorless prisms or needles with exception of the hydrochlorides (3·HCl and 17·HCl) which had a yellowish color. [b] See ref. 21 in Experimental. [c] The hydrochloride was prepared directly from the crude base. [d] In addition some cyclized material (IV-35) was isolated.

TABLE III

BENZODIAZEPINONES (IV AND V)

(in IV R_2 = H)



	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	Method	Cryst. from[a]	M.p., °C.	Yield,[b] %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	H	H	H	H	H	H	H	H	H	Q[d]			68					
										L[c]	alc.	178–179	85.5	$C_{15}H_{12}N_2O$	76.25	5.12	76.08	5.03
2	CH_3	H	H	H	H	H	H	H	H	S	alc.	154–156	44	$C_{16}H_{14}N_2O$	76.8	5.58	76.79	5.64
3[e]	H	H	H	Cl	H	H	H	H	H	L[f,g]			33					
										Q			52					
4[e]	CH_3	H	H	Cl	H	H	H	H	H	H[h]			73					
5[e]	$C_6H_5CH_2$	H	H	Cl	H	H	H	H	H	L			60.2					
6	CH_2=CH—CH_2	H	H	Cl	H	H	H	H	H	L	h.	105–106	57	$C_{18}H_{15}ClNO_2$	69.56	4.87	49.89	5.09
7	H	H	H	Cl	H	H	H	H	CH_3	L[i]			75					
										Q_1	b. + p.	220–221	24	$C_{16}H_{13}ClNO_2$	67.49	4.60	67.28	4.40
8	H	H	H	Cl	H	H	H	H	$CH(CH_3)_2$	Q_1	e. + p.	226–227	8.7	$C_{18}H_{17}ClN_2O$	69.12	5.48	69.39	5.77
9	H	H	H	Cl	H	H	H	H	$CH_2CH(CH_3)_2$	Q_1	$CHCl_3$ + h.	213–214	15	$C_{19}H_{19}ClN_2O$	69.82	5.86	69.92	5.97
10	H	H	H	Cl	H	H	H	H	CH_2OCH_3	Q_1	e.	166–167	10	$C_{17}H_{15}ClN_2O_2$	64.87	4.80	64.83	4.98
11	H	H	H	Cl	H	H	H	H	CH_2—CH_2—SCH_3	Q_1	alc.	179–180	7	$C_{18}H_{17}ClN_2OS$	62.69	4.97	62.73	5.02
12	H	H	H	Cl	H	H	H	H	C_6H_5	Q_1	DMF	269–270	52.3	$C_{21}H_{15}ClN_2O$	72.73	4.36	72.51	4.37
13	H	H	H	Cl	H	H	H	H	$CH_2C_6H_4OH(p)$	Q_1	b.	151–153	42	$C_{22}H_{17}ClN_2O_2$	70.12	4.55	70.32	4.59
14	H	H	Cl	H	H	H	H	H	H	Q[d]	ac.	214–215	30	$C_{15}H_{11}ClN_2O$	66.55	4.10	66.43	4.07
15	H	H	H	H	Cl	H	H	H	H	Q[d]	b. + h.	244–245	18	$C_{15}H_{11}ClN_2O$	66.55	4.10	66.09	4.21
6	H	Cl	H	H	H	H	H	H	H	R			25					
										L	ac. + h.	175–176	20	$C_{15}H_{11}ClN_2O$	66.55	4.10	66.68	4.44
17	H	H	H	F	H	H	H	H	H	N	ac. + p.	197–198	76	$C_{15}H_{11}FN_2O$	70.86	4.36	70.91	4.14
17a	CH_3	H	H	F	H	H	H	H	H	S	e.	109–110	60	$C_{16}H_{13}FN_2O$	71.63	4.88	71.83	4.64
18	H	H	H	H	H	F	H	H	H	N	ac. + h.	180–181	77	$C_{15}H_{11}FN_2O$	70.86	4.36	70.64	4.48
19	CH_3	H	H	H	H	F	H	H	H	U	e.	113–114	44	$C_{16}H_{13}FN_2O$	71.65	4.89	71.32	4.86
20	H	H	H	Br	H	H	H	H	H	Q[d]			15					
										N	ac.	220–221	76	$C_{15}H_{11}BrN_2O$	57.16	3.52	57.16	3.63
21	H	Cl	H	Cl	H	H	H	H	H	Q[d]			10					
										L	ac.	207–208	40	$C_{15}H_{10}Cl_2N_2O$	59.03	3.30	58.88	3.16
22	H	H	H	Cl	H	H	H	Cl	H	Q[d]			70					
										N_1	alc.	247–248	51	$C_{15}H_{10}Cl_2N_2O$	59.03	3.30	59.33	3.51
22a	CH_3	H	H	Cl	H	H	H	Cl	H	S	e.	154–156	74	$C_{16}H_{21}Cl_2N_2O$	60.21	3.79	59.94	4.10
22b	C_2H_5	H	H	Cl	H	H	H	Cl	H		alc.	128.5–129.5	74	$C_{17}H_{14}Cl_2N_2O$	61.28	4.23	61.53	4.56
22c	CH_2=CH—CH_2	H	H	Cl	H	H	H	Cl	H		CH_2Cl_2 + p.	145–146	85	$C_{18}H_{14}Cl_2N_2O$	62.62	4.09	62.68	4.36

TABLE III (*continued*)

	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	Method	Cryst. from[a]	M.p., °C.	Yield,[b] %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
23	H	H	H	Cl	H	Cl	H	H	H	N[1] M R[j]	alc.	199–201	75 50 15	$C_{15}H_{10}Cl_2N_2O$	59.03	3.30	58.74	3.02
24	CH_3	H	H	Cl	H	Cl	H	H	H	S	alc. + p.	135–136	78	$C_{16}H_{12}Cl_2N_2O$	60.21	3.79	59.98	3.95
25	CH—$(CH_3)_2$	H	H	Cl	H	Cl	H	H	H	S[k]	e.	148–150	17	$C_{18}H_{16}Cl_2N_2O$	62.26	4.64	62.02	4.84
26	CH_2—CH=CH_2	H	H	Cl	H	Cl	H	H	H	S[k]	alc.	128–130	40	$C_{18}H_{14}Cl_2N_2O$	62.62	4.09	62.79	4.27
27	H	H	H	Cl	H	F	H	H	H	L[f] N[1] R	b. + h.	205–206	72 90 47.6	$C_{15}H_{10}ClFN_2O$	62.40	3.49	62.17	3.43
28	CH_3	H	H	Cl	H	F	H	H	H	S	m. + H_2O	69–74	81	$C_{16}H_{12}ClFN_2O$	63.48	4.00	63.23	4.11
29	H	H	H	Cl	H	H	F	H	H	R	ac.	200–201	47	$C_{15}H_{10}ClFN_2O$	62.40	3.49	62.51	3.63
30	H	H	H	Cl	H	H	H	F	H	N	ac. + h.	223–224	75	$C_{15}H_{10}ClFN_2O$	62.40	3.49	62.71	3.31
31	H	H	H	Br	H	F	H	H	H	R O	ac. + p.	186–187	33 84	$C_{15}H_{10}BrFN_2O$	54.07	3.03	53.87	3.39
32	CH_3	H	H	Br	H	F	H	H	H	S	e.	132–133	3	$C_{16}H_{12}BrFN_2O$	55.35	3.48	55.92	4.28
33	H	H	H	Br	H	H	H	CH_3	H	Q	ac.	239–240	66	$C_{16}H_{13}BrN_2O$	58.37	3.98	58.58	3.92
34	H	H	H	Cl	H	H	CH_3	H	H	Q	b. + p.	198–199	48	$C_{16}H_{13}ClN_2O$	67.49	4.60	67.69	4.53
35	H	H	H	Cl	H	CH_3	H	H	H	N[2] R[i]	e.	180–181	88 11	$C_{16}H_{13}ClN_2O$	67.49	4.60	67.57	4.41
36	CH_3	H	H	Cl	H	CH_3	H	H	H	S	m.	137–139	90	$C_{17}H_{15}ClN_2O$	68.34	5.06	68.68	5.27
37	H	H	CH_3	CH_3	H	Cl	H	H	H	Q[l]	CH_2Cl_2 + p.	259–260	10	$C_{17}H_{15}ClN_2O$	68.34	5.06	68.01	5.18
38	H	H	H	CH_3	H	H	H	H	H	Q N	alc. + p.	208–209	44 82	$C_{16}H_{14}N_2O$	76.78	5.64	76.52	5.82
39	H	CH_3	H	CH_3	H	H	H	H	H	Q[d]	ac.	210–211	18	$C_{17}H_{16}N_2O$	77.25	6.10	77.23	6.17
40	H	H	CH_3	CH_3	H	H	H	H	H	Q[d]	m.	255–256	75	$C_{17}H_{16}N_2O$	77.25	6.10	77.20	6.35
41	H	H	H	C_6H_5	H	H	H	H	H	Q[m]	b. + p.	234–235	20	$C_{21}H_{16}N_2O$	80.74	5.16	80.90	5.30
42	H	H	OCH_3	H	H	H	H	H	H	Q[d] L	ac. + h.	186–188	20 47	$C_{16}H_{14}N_2O_2$	72.16	5.30	72.44	5.40
43	H	H	H	OCH_3	H	H	H	H	H	Q[d]	b.	217–218	26	$C_{16}H_{14}N_2O_2$	72.16	5.30	72.26	5.41
44	H	H	OCH_3	Br	H	H	H	H	H	K O	b. + h.	260–261	42 60	$C_{16}H_{13}N_2O_2Br$	55.67	3.80	56.03	3.80
45	H	H	H	Cl	H	OCH_3	H	H	H	L	alc. + H_2O	206–207	45	$C_{16}H_{13}ClN_2O_2$	63.90	4.36	63.62	4.36
46	CH_3	H	H	Cl	H	OCH_3	H	H	H	T	b. + h.	161–162	8	$C_{17}H_{15}ClN_2O_2$	64.87	4.80	65.01	4.93
47	H	H	H	Cl	H	H	H	OCH_3	H	L	b. + h.	212–214	52	$C_{16}H_{13}ClN_2O_2$	63.90	4.36	64.00	4.46
48	H	H	H	Cl	H	H	OCH_3	H	H	L	ac. + h.	219–220	54	$C_{16}H_{13}ClN_2O_2$	63.90	4.36	63.98	4.24
49	H	H	H	OH	H	H	H	H	H	Q[d]	CH_3CN	287–290	65	$C_{15}N_{12}N_2O_2$	71.47	4.80	71.67	4.72
50	H	H	H	Cl	H	OH	H	H	H	P	CH_3CN	285–287	47	$C_{15}H_{11}ClN_2O_2$	62.84	3.87	62.96	3.76

[a] ac. = acetone, alc. = ethyl alcohol, b. = benzene, DMF = dimethylformamide, e. = ether, h. = hexane, m. = methanol, p. = petroleum ether, b.p. 30–60°. The compounds formed colorless crystals with the exception of IV-50, which was yellow. [b] Many of these experiments were carried out only once and the optimal conditions were not established. This accounts for some of the low yields. [c] A mixture of 100 ml. of ether and 76 ml. of 5% methanolic ammonia was used, and the reaction mixture was worked up after 1.5 hr. [d] A second portion of 0.15 mole of glycine ester hydrochloride was added after 4 hr. It was not established whether this addition had a favorable effect on the yield. [e] Prepared by another method and described in Paper IV, L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961). [f] The chloroacetamidobenzophenone could be used in this reaction. The yield was, however, lower. [g] Ether was omitted and the mixture was left at room temperature for 5 days. This prolonged standing probably accounts for the low yield. [h] See ref. 19 in Experimental (method H). [i] The mixture was left at room temperature for 4 days. [j] See ref. 31 in Experimental (method R). [k] See ref. 32 in Experimental (method S). [l] See ref. 27 in Experimental (method Q). [m] A 0.5-mole sample of glycine ester hydrochloride was used. The reaction product was purified *via* the hydrochloride as described for IV-13, (method Q_1).

70%, starting with the amino ketones (I). When the ammonolysis of the haloacetamido compounds II was carried out in methanolic ammonia at room temperature, cyclization occurred simultaneously and the benzodiazepinones IV were the main reaction products. In some of these reactions, however, also small amounts of the aminoacetamido compounds III were obtained. We also observed under certain conditions the formation of 3-amino-4-phenyl-2(1*H*)-quinolones (VI), which will be reported elsewhere.

These compounds (III), when isolated, were separated from the less basic benzodiazepinones IV (formed simultaneously) by extraction of the crude amination mixtures with dilute mineral acid. The solutions of the more soluble aminoacetamido derivatives III were then made basic by treatment with alkali and the liberated compounds were further purified by crystallization. In some cases (II-3, 17, and 31) the crystalline hydrochlorides of III were isolated, since recrystallization of the free base III resulted in partial ring closure to IV.

Attempts to obtain the pure aminoacetamido compound from the chloro-, bromo-, or iodoacetyl-2-methylamino-5-chlorobenzophenone (II-4) resulted in mixtures. Any aminoacetamido compound (III-4) present in the reaction mixture cyclized during the working-up procedure and only the benzodiazepinone (V-4) could be isolated in pure form.

The other method for the preparation of benzodiazepinones IV was a one-step procedure in which an *o*-aminobenzophenone (I) bearing substituents in ring A or C, or both, was heated in pyridine with an excess of glycine ethyl ester hydrochloride.[8] In some cases a small amount of piperidine was used as catalyst.[9] Water and alcohol were split out and the desired benzodiazepinones (IV) were obtained in yields of 15–75%. This wide variation resulted because many of the reactions were carried out only once and no further attempts were made to establish the optimal conditions. The yields of IV-23, 35, and 37 (methods R and Q), however, are significant, since these reactions were thoroughly studied. The low yields reported in these cases are probably due to steric hindrance caused by the *ortho* substituent on the phenyl ring (R_7).

The synthesis of benzodiazepinones bearing substituents in position 3 of the hetero-ring was achieved by using salts of α-amino acid esters, other than glycine ester hydrochloride. The yields in these reactions were, however, generally quite low (IV-7–11).

Some benzodiazepinones bearing substituents in position I (V) were prepared from the corresponding haloacetamido compounds II[10] bearing a substituent on the nitrogen, or more practically, by the introduction of the 1-substituent[11] into the preformed benzodiazepinone IV. This was done by treating the sodio derivatives with methyl iodide, dimethyl sulfate, or another alkylating agent (allyl bromide, etc.). The sodio derivatives were obtained by the reaction of the benzodiazepinones with sodium methoxide in benzene, toluene, or N,N-dimethylformamide followed by removal of the liberated methanol.

The pharmacological study[2,12] of the benzodiazepinones IV and V[13] showed that this class of compounds had interesting muscle relaxant, sedative, and anticonvulsant properties. One of the most interesting compounds in the group is V-4[14] mentioned in an earlier publication.[3]

The aminoacetamido compounds III showed pharmacological properties which were similar, but generally less pronounced, than the properties of the corresponding benzodiazepinones IV. This is probably because of cyclization in the organism. This hypothesis is supported by the discovery that the sterically hindered *ortho*-substituted compounds III-23, 27, and 31 showed significantly lower pharmacological activity than the corresponding cyclization products IV.

Experimental (with B. Brust and F. Landgraf)

All melting points are corrected. The infrared spectra of starting materials and reaction products were compared in every case in order to establish or exclude structural changes. The infrared spectra were determined in 1–5% chloroform solution using a Perkin Elmer Model 21 spectrophotometer.

2-Haloacetamidobenzophenones (II) (Table I). Method A.—To a stirred solution of 0.1 mole of the *o*-aminobenzophenone (I) in 500 ml. of alcohol-free ether[15] 0.13 mole of bromoacetyl bromide[16] and about 500 g. of ice were added simultaneously and in portions, the reaction temperature being kept at 10–15°. The completion of the reaction (1–2 hr.) was indicated by the disappearance of the yellow color of the aminobenzophenone in the ether solution. The organic layer was separated, washed with water, cold dilute sodium hydroxide solution, or cold dilute aqueous ammonia, dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crystalline residue was recrystallized to yield colorless prisms or needles of the 2-haloacetamidobenzophenone.

Method B.—To a stirred, cooled (10°) solution of 0.1 mole of the 2-aminobenzophenone in 400 ml. of dioxane,

(8) Glycine hydrochloride or glycine methyl ester hydrochloride gave lower yields. This was established in experiments leading to IV-3.

(9) The favorable effect of the piperidine catalyst was studied in the case of IV-27.

(10) The corresponding N-substituted *o*-aminobenzophenones (I-4, 5–6) are described in paper V.[1]

(11) The structure of these compounds was confirmed by the lack of the NH band at 3300–3430 cm.$^{-1}$ in the infrared spectrum and the presence of the characteristic, very strong, carbonyl band at around 1700 cm.$^{-1}$.

(12) Further pharmacological studies will be reported elsewhere by L. O. Randall *et al.*

(13) Compound V-2 was prepared by Mr. O. Keller, and IV-14 by Dr. G. Saucy.

(14) Valium.®

(15) The amount of the ether was varied, and in some cases benzene was used as the solvent. When concentrated solutions were used, part of the reaction product crystallized in almost chemically pure form and was separated by filtration. The mother liquor was worked up as above.

(16) In the preparation of II-4 Cl, -23 Cl, and -27 Cl, chloroacetyl chloride was used.

0.13 mole of the α-haloacyl halide (the two halogens were the same), and an equivalent amount of 3 *N* sodium hydroxide was added in small portions. The two reactants were introduced alternately at such a rate as to keep the temperature below 10° and the mixture neutral or slightly alkaline. The reaction was completed after 30 min. The neutral mixture was diluted with ice and water, and extracted with methylene chloride. The extract was washed with water, dried, filtered, concentrated *in vacuo*, and the residue crystallized.

Method C.—A solution of 0.04 mole of 2-(N-methylchloroacetamido)-5-chlorobenzophenone in 100 ml. of acetone containing 0.044 mole of sodium iodide was refluxed for 20 min. After cooling, the inorganic salts were removed by filtration and the acetone was evaporated *in vacuo*. The residue was dissolved in a mixture of benzene and petroleum ether, filtered again to remove the remaining inorganic salts, and concentrated in vacuo. The residue was crystallized to give the desired product.

Method D.—A solution of 0.1 mole of the aminobenzophenone and 0.2 mole of bromoacetyl bromide in 200 ml. of benzene was refluxed for 2 hr. to expel most of the formed hydrogen bromide. The solution was then cooled, washed with ice cold alkali, and worked up as in method A.

Method E.—A solution of 0.1 mole of the aminobenzophenone, 0.12 mole of bromoacetyl bromide, and 0.1 mole of pyridine in 450 ml. of ether was kept at room temperature for 2 hr. The ether solution was then washed several times with water, dried, and concentrated *in vacuo*. The reaction product which crystallized during the concentration was separated by filtration and recrystallized.

Method F.—The *o*-acetamidobenzophenone[17] was used as starting material. It was first hydrolyzed by refluxing with a thirtyfold amount of a 2:1 mixture (volume/volume) of ethanol and 6 *N* hydrochloric acid. The mixture was concentrated *in vacuo*, neutralized, and the *o*-aminobenzophenone extracted with ether and then processed without further purification as described in method A. The yields shown in the table include both steps.

2-Aminoacetamidobenzophenones (III). Method G.—A stirred suspension of 0.1 mole of the 2-bromoacetamidobenzophenone in 800 ml. of liquid ammonia was refluxed for 5 hr., then the ammonia was allowed to evaporate (about 15 hr.). The crude aminoacetamidobenzophenone thus obtained was ground, washed with water to remove the admixed ammonium bromide, and dried.[18] This crude product could be recrystallized to yield pure aminoacetamidobenzophenone.

In most cases, however, the material was contaminated with small amounts of the corresponding benzodiazepinones formed simultaneously. Purification was effected by the following method: The crude dry aminoacetamido compound was dissolved in methylene chloride. This solution was then extracted with a smaller than calculated amount (80–90%) of 0.3 *N* hydrochloric acid in which the more basic aminoacetamido compound was readily soluble. The acidic solution was then made basic with dilute ammonia and extracted with ether or methylene chloride. The organic layer was concentrated *in vacuo* and the residue recrystallized *without heating* (heating in solvents caused ring closure).

Method H.—To a solution of 0.02 mole of the bromoacetamidobenzophenone in 100 ml. of methylene chloride 100 ml. of liquid ammonia was added. The mixture was stirred for 5 hr. while the ammonia was refluxing (Dry Ice condenser), then the ammonia was evaporated at room temperature.[19] The methylene chloride solution was washed with water, dried, and evaporated *in vacuo*. The residue was recrystallized.

Hydrochloride of 2-Aminoacetamidobenzophenones (III-HCl). Method J.—The base was dissolved in a tenfold amount of methanol containing 1:2 equivalents of hydrogen chloride. Ether was added, the mixture was cooled, and the crystalline precipitated salt was separated by filtration and recrystallized from the same solvent mixture. The pure hydrochloride gave a clear aqueous solution, and any turbidity indicated the presence of benzodiazepinone (IV). This contamination, if present, was removed by extraction of the aqueous solution with methylene chloride. The solution was then made alkaline and the free aminoacetamidobenzophenone (III) extracted with methylene chloride. The methylene chloride solution was dried, concentrated *in vacuo*, and the residue converted again to the salt as described above.

5-Bromo-2-aminoacetamido-4-methoxybenzophenone (III-44) and 7-Bromo-1,3-dihydro-8-methoxy-5-phenyl-2H-1,4-benzodiazepin-2-one (IV-44). Method K.—A suspension of 0.01 mole of 5-bromo-2-bromoacetamido-4-methoxybenzophenone in 200 ml. of a 20% (w./v.) solution of ammonia in methanol was stirred for 24 hr. at room temperature. The precipitated 5-bromo-2-aminoacetamido-4-methoxybenzophenone (III-44) was separated by filtration. After recrystallization the product melted at 161–163°, resolidified at 165–168°, and then remelted at 248–251°. The methanolic ammonia filtrate obtained after the separation of III-44 was concentrated to dryness *in vacuo*, and the residue recrystallized to give IV-44.

1,3-Dihydro-5-phenyl-2H-1,4-benzodiazepin-2-ones (IV and V)[20] from *o*-Haloacetamidobenzophenones (III). Method L.—*o*-Bromoacetamidobenzophenone[21] (0.005 mole) was dissolved at room temperature in a mixture of 100 ml. of ether[22] and 60 ml. of a 13% (w./w.) solution of ammonia in methanol. After 18 hr. the solution was concentrated to dryness *in vacuo* in a water bath below 25°.[23] The residue was partitioned[24] between ether and water or methylene chloride and water. The organic layer was separated, dried, concentrated *in vacuo*, and the residue recrystallized.

Method M.—A solution of 2-chloroacetamido-2′,5-dichlorobenzophenone (50 g.) in 500 ml. of dimethylformamide was cooled to −30° and 200 ml. of liquid ammonia was added. The solution was kept at −33° for 5 hr. and then the ammonia was allowed to evaporate overnight. Dimethylformamide was removed *in vacuo* and the residue, consisting of a mixture of III-23 and IV-23, was refluxed with pyridine for 20 hr. in order to cyclize the aminoacetamido compound, III-23. The pyridine was removed *in vacuo* and the residue treated with sodium bicarbonate solution and benzene. Part of the reaction product crystallized and was separated by filtration. The benzene layer was washed with water and concentrated *in vacuo*. The residue was recrystallized together with the solid material which had been separated.

1,3-Dihydro-5-phenyl-2H-1,4-benzodiazepin-2-ones (IV) from 2-Aminoacetamidobenzophenones (III). Methods N, N_1, and N_2.—A solution of 0.05 mole of the 2-aminoacetamidobenzophenone (III) in 200 ml. of a solvent was refluxed and then concentrated *in vacuo*. The residue was crystallized. Specific data are given below.

(17) 2′-Acetamido-5-chloro-3′-methoxybenzophenone leading to II-48 was prepared by the method of Lothrop and Goodwin.[8] It was not obtained crystalline but was used without further purification in the synthesis of the corresponding bromoacetamido derivative.

(18) Such material was used for the cyclization described in method N, and for the preparation of the hydrochloride III-17·HCl.

(19) Attempts to prepare the aminoacetamido compound III-4 by this method from the bromo- or iodoacetamido compound II-4 resulted only in the isolation of the cyclized V-4.

(20) Compounds of formula V were obtained when haloacetamido N-substituted aminobenzophenones were used.

(21) In an attempt to prepare IV-15 by this method cyclization did not occur. The crude amorphous residue yielded only the aminoacetamido derivative (III-15). The crude material was dissolved in a benzene–hexane mixture (1:1) and purified by chromatography on a fifteenfold amount of activated alumina (Woelm, neutral, grade III). The material was eluted with the same solvent mixture and was crystallized after removal of the solvents.

(22) In some cases the ether was omitted.

(23) Hydrolysis to the aminobenzophenone occurred if the temperature were too high.

(24) In some cases part of the reaction product remained undissolved. It was separated by filtration and recrystallized.

Method N.—Crude aminoacetamidobenzophenone obtained as described in method G (see ref. 18) was dissolved in toluene, alcohol, or pyridine[25] and the solution refluxed for 1 hr. The yield shown in the table was, in these cases, based on the amount of haloacetyl-compound (II) used.

Method N_1—The solution in pyridine was refluxed for 16 hr.

Method N_2.—A solution of 0.05 mole of the aminoacetamido compound in a mixture of 750 ml. of pyridine and 50 ml. of benzene was refluxed for 75 hr. and the water which formed was removed by azeotropic distillation.

Method O.—The 2-aminoacetamidobenzophenone was fused in an oil bath at a temperature of 180°. The melt was maintained at this temperature until all evolution of water had ceased. Recrystallization of the reaction mixture yielded the cyclized product.

7-Chloro-1,3-dihydro-5-(2-hydroxyphenyl)-2H-1,4-benzodiazepin-2-one (IV-50). Method P.—2-Acetamido-5-chloro-2′-methoxybenzophenone[5] (0.03 mole) was refluxed for 8 hr. with 200 ml. of 48% hydrobromic acid. The solution was evaporated to dryness under reduced pressure and the dark residue treated with dilute ammonium hydroxide and extracted with benzene. The benzene solution was dried and the solvent removed. The crude 2-amino-5-chloro-2′-hydroxybenzophenone thus obtained was converted to the benzodiazepinone IV-50, without purification of intermediates, by forming the bromoacetamido derivative II (method B) and ammonolysis with concomitant ring closure (method L).

1,3-Dihydro-5-phenyl-2H-1,4-benzodiazepin-2-ones from 2-Aminobenzophenones and Glycine Ethyl Ester Hydrochloride. Method Q.—A solution of 0.1 mole of the 2-aminobenzophenone and 0.15 mole of glycine ethyl ester hydrochloride[26] in 200 ml. of pyridine was refluxed for 15 hr.[27] During the first 4 hr. 20–50 ml. of the solvent was slowly distilled and replaced by fresh dry pyridine. This was done in order to remove some of the water and alcohol formed during the reactions.[28]

After 15 hr., the mixture was concentrated *in vacuo* and the residue partitioned between ether and water. In most cases some of the reaction product remained undissolved and was separated by filtration. The aqueous layer was made alkaline (benzodiazepinones are weak bases, and partly soluble in the hydrochloric acid derived from the glycine ester hydrochloride) and extracted with ether. The ether layers were combined, washed, dried, and concentrated. The reaction product was separated from the unchanged amino ketone[29] by crystallization. The fractions of crystalline reaction product were combined and purified by crystallization, if necessary with the addition of activated charcoal.

3-Substituted 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-ones. Method Q_1.—For the preparation of IV-7 to 13 the reaction was carried out as described under Q using the α-amino acid ester hydrochloride shown below, instead of glycine ethyl ester hydrochloride.

IV-7.—*d,l*-α-Alanine ethyl ester hydrochloride.

IV-8.—*d,l*-Valine ethyl ester hydrochloride. The pyridine solution was refluxed for 40 hr.

IV-9.—L-Leucine ethyl ester hydrochloride. The product was purified as described under IV-13.

IV-10.—Crude O-methylserine ethyl ester hydrochloride was used. It was prepared by saturating a solution of 0.2 mole of *d,l*-O-methylserine (Mann Laboratories) in 160 ml. of absolute alcohol with hydrogen chloride, refluxing the solution for 1 hr., and concentrating it *in vacuo*. The residue then reacted as described under Q. The reaction product was extracted with benzene after concentration to a small volume, adsorbed on a column prepared with 300 g. of activated alumina containing 3% of water. Elution with 1200 ml. of benzene yielded unreacted 2-amino-5-chlorobenzophenone. Further elution with ether, methylene chloride, and methylene chloride containing 10% of methanol yielded 5 g. of the crystalline reaction product.

IV-11.—Crude *d,l*-methionine methyl ester hydrochloride was used. This was prepared by saturating a solution of 0.2 mole of *d,l*-methionine in 100 ml. of absolute methanol with hydrogen chloride, refluxing the mixture for 1 hr., and concentrating *in vacuo*.

IV-12.—*d,l*-Ethyl-α-aminophenylacetate hydrochloride.

IV-13.—L-Tyrosine ethyl ester hydrochloride was used. The mixture was refluxed for 40 hr. In order to facilitate the crystallization of the reaction product in the preparation of IV-9 and IV-13, 5 *N* aqueous hydrochloric acid was added to the ether extract which caused the precipitation of the crystalline hydrochloride of the reaction product. This was separated by filtration, decomposed with 5 *N* aqueous ammonia, and the base extracted into ether. The ether extract was concentrated *in vacuo* and the residue purified by repeated recrystallization. For IV-9 a mixture of hexane and chloroform was used for recrystallization, and for IV-13 first a mixture of ether and petroleum ether and finally benzene.

Method R.—The reaction was carried out as in Method Q with the following changes: three equivalents of glycine ester hydrochloride (0.3 mole) were used, piperidine (1–3 ml.) was added as a catalyst[30] to the pyridine, the solvent was not distilled during the reaction, and methylene chloride was used for the extraction.[31]

1-Substituted 5-Phenylbenzodiazepinones (V). Method S.—To a solution of 0.05 mole of the benzodiazepinone (IV) in 250 ml. of methanol 55 ml. of a 1 *N* solution of sodium methoxide in methanol was added. The solvent was removed *in vacuo* and the sodio derivative dissolved in 100 ml. of dimethylformamide. (The sodio derivative could also be prepared by adding to a solution of IV in DMF a 10% excess of 5 *N* methanolic solution of sodium methoxide. This solution was then used without removal of the methanol.) Keeping the reaction mixture at room temperature, 0.16 mole of methyl iodide[32] was slowly added. After stirring for 30 min., the main amount of solvent was evaporated *in vacuo* and the residue treated with water and extracted with ether or methylene chloride. The organic solution was dried, concentrated, and the residue crystallized.

Method T.—A solution of 0.02 mole of the benzodiazepinone IV-45 in 100 ml. of toluene was treated with 0.022 mole of sodium methoxide. The mixture was heated, 20 ml. of the solvent was slowly distilled in order to remove methanol, and 0.02 mole of dimethyl sulfate was added. The solution was then refluxed for 1 hr., cooled, washed with

(25) Pyridine seemed to be the best solvent for the cyclization. The most energetic conditions were used for sterically hindered compounds, (method M, N_1 and N_2).

(26) The substitution of glycine hydrochloride or glycine methyl ester hydrochloride for glycine ethyl ester hydrochloride in this reaction was studied in the synthesis of IV-3. Under conditions which gave a yield of 52% of the benzodiazepinone with glycine ethyl ester hydrochloride, glycine hydrochloride gave 10%, and glycine methyl ester hydrochloride 29%.

(27) For the preparation of IV-37, 0.2 mole of glycine ester hydrochloride was used, the distillation was omitted, and the mixture was refluxed for 48 hr. The crude reaction product was first crystallized from ether, then impurities were extracted with acetone, and the residual product was finally crystallized from dilute alcohol.

(28) It was not established in all cases whether this had a favorable effect on the yield.

(29) The crude unchanged aminobenzophenone recovered could be treated again with glycine ester hydrochloride.

(30) If the piperidine was omitted in the preparation of IV-27 no product was obtained. With quinoline, 3% in pyridine, the yield (25%) was much lower than that obtained with piperidine (47.5%).

(31) In the preparation of IV-23 and 35, ether was used for extraction. The acid soluble benzodiazepinone formed in low yield was separated from the unreacted aminobenzophenone by extraction of the ether solution with 2 *N* hydrochloric acid. The acidic solution was then neutralized and the product extracted with ether.

(32) In V-22b and c, ethyl iodide and allyl bromide were used, respectively. In the preparation of V-25, isopropyl iodide, and V-26 allyl bromide was used. The reaction time in the two latter experiments was 2 hr. and the temperature 50°.

water, dilute sodium hydroxide, dried, and concentrated *in vacuo*. The residue was treated with a mixture of 25 ml. of benzene and 50 ml. of hexane, and undissolved starting material was removed by filtration. The solution was then adsorbed on a column of 50 g. of activated alumina (Woelm, neutral, grade I) and the product eluted with benzene.[33] The combined benzene eluates were concentrated *in vacuo* and the residue crystallized.

Method U.—A 50% suspension of sodium hydride in heavy mineral oil, (0.13 mole) was added portionwise to a stirred solution of 1,3-dihydro-5-(2-fluorophenyl)-2*H*-1,4-benzodiazepin-2-one (0.12 mole) in 60 ml. of dimethylformamide. The mixture was stirred for 15 min. in the cold, then 0.142 mole of methyl iodide was added and the solution stirred for 20 min. more. The solvent was removed under reduced pressure to yield an oil which was partitioned between water and methylene chloride. The organic layer was washed, dried, and filtered. Removal of the solvent gave an oil which was taken up in ether and filtered through alumina (Woelm, Grade I). The colrrless filtrate was concentrated and the residue crystallized.

(33) Further elution with benzene containing 5% ethanol gave unreacted starting material.

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Borohydride Reductions of 8-Oxodecahydronaphthoic Acids and Esters[1]

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The action of sodium borohydride on *cis*- and *trans*-8-oxodecahydronaphthoic acids and their methyl esters has been studied. The results suggest that a carboxylate ion can inhibit the attack of borohydride ion.

As part of a study of the stereochemistry of the lactone ring of marrubiin,[3] we wished to reduce the keto acid (Ia) stereospecifically to the alcohols (IIa) and (III) and then to observe the relative ease with which these hydroxy acids lactionized. The keto acid (Ia) has now been synthesized and reduced to the alcohol (IIa) but not to III. The work has been extended to include a study of the reactions of the keto acid (VIIIa) and the keto esters (Ib) and (VIIIb) with sodium borohydride.

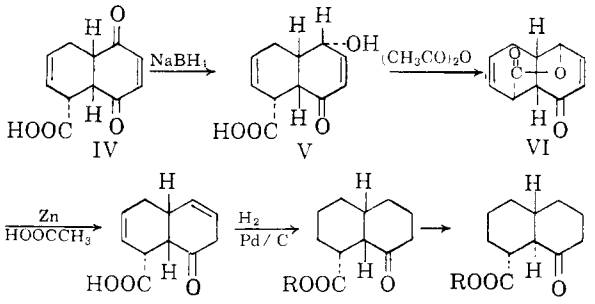

CHART I

The keto acid (VIIIa) was synthesized from the Diels-Alder adduct (IV, from pentadienoic acid and *p*-benzoquinone) by the route shown in Chart I. The stages IV–VII had previously been reported by Woodward and co-workers.[4] Some minor clarifications of their work are mentioned in the Experimental. In the presence of palladium VII took up two moles of hydrogen and yielded VIIIa. The stereochemistry of VIIIa follows from the stereochemistry of VI.[4] The possibility that the ring fusion had become *trans* during the conversion of VI to VIIIa was obviated when it was found that VIIIa, when heated with base, was isomerized to a new compound which was, therefore, assigned the structure Ia. Both Ia and VIIIa were converted to the corresponding methyl esters (Ib) and (VIIIb) by treatment with diazomethane. The infrared spectra and analyses of Ia, Ib, VIIIa, and VIIIb were all consistent with the assigned structures.

Reduction Studies.—The reduction of Ia was attempted under three sets of conditions, (a) sodium and propanol (b) lithium, methanol and liquid ammonia, and (c) sodium borohydride in bicarbonate solution at 0°. In all reactions only one product was isolated—a hydroxy acid—which, because it was formed under conditions (a) in 50% yield and under conditions (b) in 90% yield, was assigned the structure IIa,[5,6] in which the hydroxyl group is equatorial. As expected, the hydroxy acid (IIa) lactonized readily to yield IX.

(1) For a preliminary account see D. M. S. Wheeler and M. Wheeler, *Chem. Ind.* (London), 463 (1961).

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(3) W. H. Castine, D. M. S. Wheeler, and M. Wheeler, *Chem. Ind.* (London), 1832 (1961).

(4) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958).