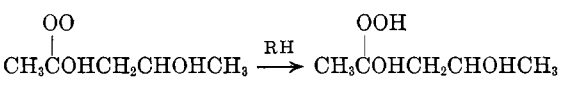
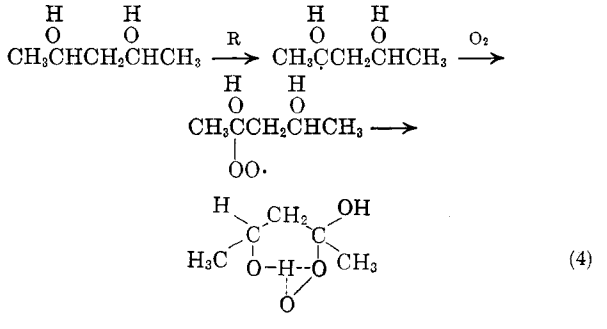
is attacked and the products are principally 4-hydroxy-2-pentanone and water. Most notable, however, are the very low yields of hydrogen peroxide in contradistinction to the semiquantitative yields obtained from the monohydroxy compounds. These minimal yields indicate that for some reason the usual chain propagation step is taking place only with considerable difficulty. Nor is this reduction



in yield a consequence of any unusual instability of hydrogen peroxide in the diol, as comparative peroxide decomposition rates in the diol and in 2-propanol show that hydrogen peroxide is even less stable in 2-propanol from which high peroxide yields are obtainable on autoxidation.

Therefore, the pentanediol peroxy radical must differ markedly from the peroxy radicals derived from the substituted pentanols.

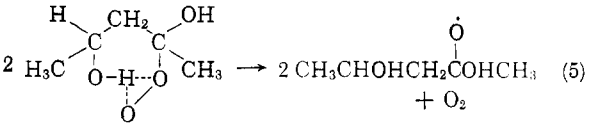
Again, to rationalize these findings, it is concluded that in the case of the mono-ols, chain propagation involves *intermolecularly* bonded peroxy radicals



(4)

whereas in the case of the 2,4-diol *intramolecularly* hydrogen bonded radicals are the important product determinants.

Subsequent peroxy radical–peroxy radical interaction should assume increased importance because of the augmented radical stability brought about by hydrogen bonding. The resultant two oxy radicals and oxygen (equation 5) would then lead to the main final products, keto alcohol and water, without formation of peroxide.



(5)

The relatively small amount of peroxide actually found is presumably a consequence of chain propagation by the more conventional intermolecularly hydrogen bonded peroxy groups.

The above conclusions receive support from the work of Denisov[6] which shows that the kinetics of the autoxidation of cyclohexanone can be altered by the presence of water. He concludes that a reduced rate is brought about by hydrogen bonding between the peroxy radicals and water.

Acknowledgment.—The authors gratefully acknowledge the assistance of Mr. C. S. Bell who synthesized 4-methoxy-2-pentanol and 2,4-dimethoxypentane, and helpful suggestions of Dr. J. K. Kochi.

(6) E. T. Denisov, *Izv. Akad. Nauk SSSR Otd. Khim. Nauk*, P 53 (1960).

Quinazolines and 1,4-Benzodiazepines. V. *o*-Aminobenzophenones[1a,b]

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A series of substituted *o*-aminobenzophenones was prepared. Some of these compounds were converted *via* their tosyl derivatives into N-monosubstituted *o*-aminobenzophenones. These primary and secondary amines were needed as intermediates for the synthesis of 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones.[1c]

Several new substituted *o*-aminobenzophenones needed for the synthesis of 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones[2] were prepared according to the methods outlined below.

The first method (A) employed was the condensation of a *para*-substituted aniline (I) with benzoyl chloride or a substituted benzoyl chloride (II) using zinc chloride as a catalyst, followed by energetic hydrolysis of the primary reaction product which was not isolated.[3,4] Compounds IIIa–IIIg shown in Table I were obtained by this method.

(1) (a) Paper IV. L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961). (b) 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. (c) The nomenclature for the 1,4-benzodiazepines was adopted after consultation with Dr. L. T. Capell of *Chemical Abstracts*.

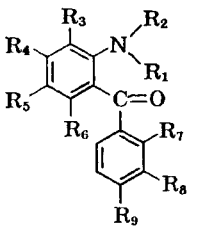
(2) L. H. Sternbach, R. Ian Fryer, W. Metlesics, E. Reeder, G. Sach, L. G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).

(3) K. Dziewoński and L. H. Sternbach, *Bull. intern. acad. polon., Classe sci. mat. nath., Ser. A*, 333–348 (1935); *Chem. Abstr.*, **30**, 2972 (1936).

(4) L. H. Sternbach, E. Reeder, O. Keller, and W. Metlesics, *J. Org. Chem.*, **26**, 4488 (1961).

TABLE I

SUBSTITUTED *o*-AMINOBENZOPHENONES

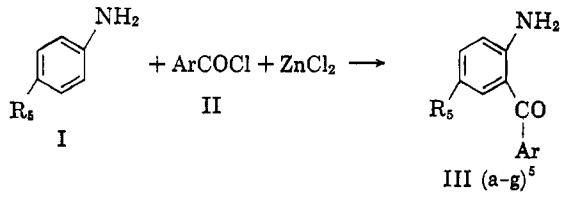


	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	Method	Cryst.[a] from	Color, shape	M.p.	Yield[b]	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
IIIa	H	H	H	H	Cl	H	F	H	H	A	M	Yellow needles	94–95°	77%	$C_{13}H_9NOClF$	62.54	3.63	62.84	3.76
IIIb	H	H	H	H	Cl	H	H	F	H	A	M	Yellow needles	90–91°	60%	$C_{13}H_9NOClF$	62.54	3.63	62.34	3.66
IIIc	H	H	H	H	Cl	H	H	H	F	A_1	H	Yellow needles	108–109°	65%	$C_{13}H_9NOClF$	62.54	3.63	62.71	3.64
IIId	H	H	H	H	Br	H	F	H	H	A_2	M	Yellow needles	101–102°	64%	$C_{13}H_9NOBrF$	53.08	3.09	53.16	2.78
IIIe	H	H	H	H	Cl	H	CH_3	H	H	A_3	Hept.	Yellow crystals	50–55°	60%	$C_{14}H_{12}NOCl$	68.43	4.92	68.20	5.27
IIIf[c]	H	H	H	H	Cl	H	H	CH_3	H	A_4	E + P	Yellow prisms	90–91°	40%	$C_{14}H_{12}NOCl$	68.43	4.92	68.59	4.71
IIIg	H	H	H	H	C_6H_5	H	H	H	H	A_5	Alc. + P	Yellow needles	112–113°	24%	$C_{19}H_{15}NO$	83.49	5.53	83.38	5.23
VIIh	H	Ac	Cl	H	H	H	H	H	H	B	CH_2Cl_2 + H	Colorless crystals	129–131°	25%	$C_{15}H_{12}NO_2Cl$	65.82	4.42	65.74	4.67
VIIi	H	Ac	H	H	OCH_3	H	H	H	H	B	B, H	Colorless plates	131–132°	51%	$C_{16}H_{15}NO_3$	71.36	5.61	71.44	5.52
VIIj	H	Ac	H	H	Cl	H	OCH_3	H	H	B	H	Colorless crystals	124–126°	22%	$C_{16}H_{14}NO_3Cl$	63.27	4.65	63.34	4.49
VIIk	H	Ac	H	H	Cl	H	H	H	OCH_3	B	D alc.	Colorless crystals	148–149°	17%	$C_{16}H_{14}NO_3Cl$	63.27	4.65	64.32	5.24
IXi	H	H	H	H	OCH_3	H	H	H	H	B	P	Yellow crystals	51–52°	16%	$C_{14}H_{13}NO_2$	73.99	5.77	74.01	5.64
IXj	H	H	H	H	Cl	H	OCH_3	H	H	B	E + H	Yellow prisms	81–83°	20%	$C_{14}H_{12}CCNO_2$	64.25	4.62	64.51	4.63
IXl	H	H	H	H	H	Cl	H	H	H	B	H	Yellow crystals	101–102°	25%	$C_{13}H_{10}NOCl$	67.39	4.35	67.49	4.03
IXm	H	H	H	Cl	H	H	H	H	H	B	H	Sl. yellow needles	84–85°	40%	$C_{13}H_{10}NOCl$	67.39	4.35	67.51	4.20
Xn	H	H	H	H	OH	H	H	H	H	E	B, H	Reddish yellow crystals	127–128°	85%	$C_{13}H_{11}NO_2$	73.22	5.20	73.56	5.44
XIIo	H	Ac	H	OCH_3	H	H	H	H	H	C	D alc.	Colorless plates	118–119°	6%	$C_{16}H_{15}NO_3$	71.36	5.61	71.55	5.37
XVp	H	Ac	H	OCH_3	Br	H	H	H	H	D	D alc.	Colorless crystals	144–145°	85%	$C_{16}H_{14}NO_3Br$	55.18	4.05	55.91	4.11
XVIp	H	H	H	OCH_3	Br	H	H	H	H	D	B, H	Sl. yellow crystals	151–152°	83%	$C_{14}H_{12}NO_2Br$	54.92	3.95	54.96	4.16
XXq	H	Benzoyl	H	H	H	H	F	H	H	F	H	Colorless needles	113–114°	86.5%	$C_{20}H_{14}NO_2F$	75.22	4.42	75.54	4.56
XXIq	H	H	H	H	H	H	F	H	H	F	Alc.	Yellow prisms	126–128°	98%	$C_{13}H_{10}MOF$	72.55	4.68	72.66	4.40
XXIIa	Ts	H	H	H	Cl	H	F	H	H	C	M	Yellow prisms	119–120°	92%	$C_{20}H_{15}NO_3ClFS$	59.48	3.74	59.65	3.83
XXIIb	Ts	H	H	H	Cl	H	H	F	H	C	M	Colorless needles	132–133°	86%	$C_{20}H_{15}NO_3ClFS$	59.48	3.74	59.65	4.11
XXIIc	Ts	H	H	H	Cl	H	H	H	F	G	Alc.	Colorless prisms	126–128°	94%	$C_{20}H_{15}NO_3ClFS$	59.48	3.74	59.32	3.87
XXIId	Ts	H	H	H	Br	H	F	H	H	G	M	Colorless prisms	114–115°	81%	$C_{20}H_{15}NO_3BrFS$	53.58	3.39	53.83	3.47
XXIIq	Ts	H	H	H	H	H	F	H	H	G	Alc.	Colorless needles	129–130°	87%	$C_{20}H_{16}NO_3FS$	65.03	4.11	65.46	4.34
XXIIr	Ts	H	H	H	Cl	H	H	H	H	G	Alc.	Colorless needles	120–121°	85%	$C_{20}H_{16}NO_3ClS$	62.25	4.18	62.10	4.44
XXIIs	Ts	H	H	H	Cl	H	Cl	H	H	G	Alc.	Colorless crystals	136–138°	79%	$C_{20}H_{15}NO_3Cl_2S$	57.15	3.60	57.16	3.85
XXIIt	Ts	H	H	H	Br	H	H	H	H	G	E + P	Colorless needles	117–118°	87%	$C_{20}H_{16}NO_3BrS$	55.82	3.75	56.02	4.06
XXIIIa	Ts	CH_3	H	H	Cl	H	F	H	H	H	E	Colorless needles	149–150°	85%	$C_{21}H_{17}NO_3ClFS$	60.36	4.10	60.21	4.12
XXIIId	Ts	CH_3	H	H	Br	H	F	H	H	H	Alc.	Colorless needles	154–155°	86%	$C_{21}H_{17}NO_3BrFS$	54.55	3.71	54.62	3.83
XXIIIr	Ts	Na	H	H	Cl	H	H	H	H	G_1	DMF + $CHCl_3$	Yellow needles	298–299°	85%	$C_{20}H_{15}NO_3ClSNa$	58.90	3.71	59.05	3.96
XXIIIr$_1$	Ts	CH_3	H	H	Cl	H	H	H	H	H_2	Alc.	Colorless needles	151–152°	86%	$C_{21}H_{18}NO_3ClS$	63.07	4.54	62.85	4.69
XXIIIr$_2$	Ts	C_6H_5	H	H	Cl	H	H	H	H	H_2		[d]							

Table I (*continued*)

	R_1	R_3	R_4	R_5	R_6	R_7	R_8	R_9	Method	Cryst.[a] from	Color, shape[d]	M.p.	Yield[b]	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
XXIIIr[3]	Ts	Allyl	H	H	Cl	H	H	H	H_2									
XXIIIr[4]	Ts	Benzyl	H	H	Cl	H	H	H	H_4	E, H	Colorless prisms	116–118°	96%	$C_{27}H_{22}NO_3ClS$	68.13	4.66	68.25	4.76
XXIIIs	Ts	CH_3	H	H	Cl	H	Cl	H	H_1	M	Colorless crystals	145–153°	78%	$C_{21}H_{17}NO_3Cl_2S$	58.07	3.95	58.45	3.94
XXIIIt	Ts	CH_3	H	H	Br	H	H	H	H_2		[d]							
XXIVa	H	CH_2	H	H	Cl	H	F	H	J	M	Yellow prisms	118–119°	92%	$C_{14}H_{11}NOClF$	63.77	4.20	63.28	4.28
XXIVd	H	CH_3	H	H	Br	H	F	H	J	E	Yellow needles	112–113°	50%	$C_{14}H_{11}NOBrF$	54.57	3.60	54.59	3.85
XXIVr[1]	H	CH_3	H	H	Cl	H	H	H	J	Alc. + P	Yellow plates	94–95°	95%	$C_{14}H_{12}NOCl$	68.43	4.92	68.29	5.08
XXIVr[2]	H	C_2H_5	H	H	Cl	H	H	H	J_2	M	Yellow prisms	56–57°	45%	$C_{15}H_{14}NOCl$	69.36	5.43	69.50	5.41
XXIVr[3]	H	Allyl	H	H	Cl	H	H	H	J_2	M	Yellow needles	76–77°	67%	$C_{16}H_{14}NOCl$	70.72	5.19	70.47	5.33
XXIVr[4]	H	Benzyl	H	H	Cl	H	H	H	J	Alc.	Yellow prisms	86–87°	33%	$C_{20}H_{16}NOCl$	74.65	5.01	74.90	5.01
XXIVs	H	CH_3	H	H	Cl	H	Cl	H	J_1	E, H	Yellow crystals	88–90°	85%	$C_{14}H_{11}NOCl_2$	60.02	3.96	59.96	4.12
XXIVt	H	CH_3	H	H	Br	H	H	H	J	P	Yellow needles	97–98°	52%	$C_{14}H_{12}NOBr$	57.95	4.17	58.04	4.10
XXVIr	CH_3	CH_3	H	H	Cl	H	H	H	K	Alc.	Yellow prisms	91–92°	59%	$C_{15}H_{14}NOCl$	69.36	5.43	69.64	5.27

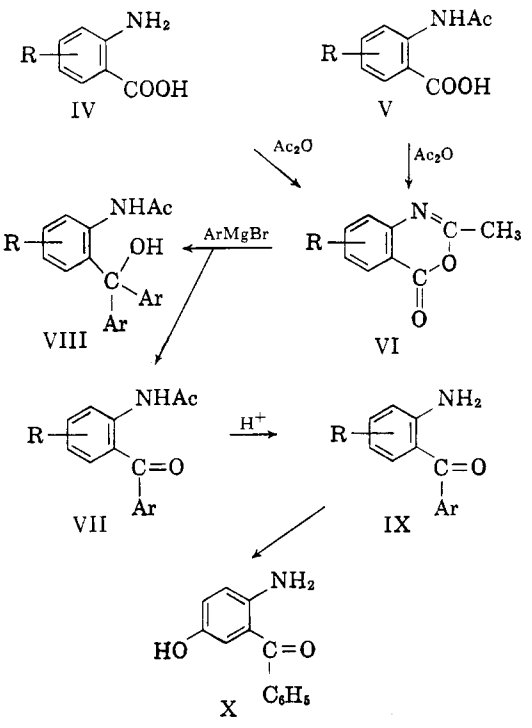
[a] Alc. = ethyl alcohol, B = benzene, D alc. = dilute ethyl alcohol, DMF = dimethylformamide, E = ether, Hept. = heptane, H = hexane, M = methyl alcohol, P = petroleum ether, b.p. 30–60°. [b] Many of these experiments were carried out only once and the optimal conditions were not established. This accounts for some of the low yields. [c] This compound was prepared by Mr. N. Takahashi. [d] The product formed a yellowish oil and was used in the next step without further purification. [e] Two steps, see footnote *c*.



I II III (a-g)[5]

Ar = phenyl or a monosubstituted phenyl
R_5 has the same meaning as in the tables

A second convenient approach (method B) to substituted *o*-aminobenzophenones was the method of Lothrop and Goodwin[6] following the reaction sequence shown below:



IV V VIII VI VII IX X

Ac = acetyl
Ar = phenyl or methoxyphenyl
R = chlorine or methoxyl

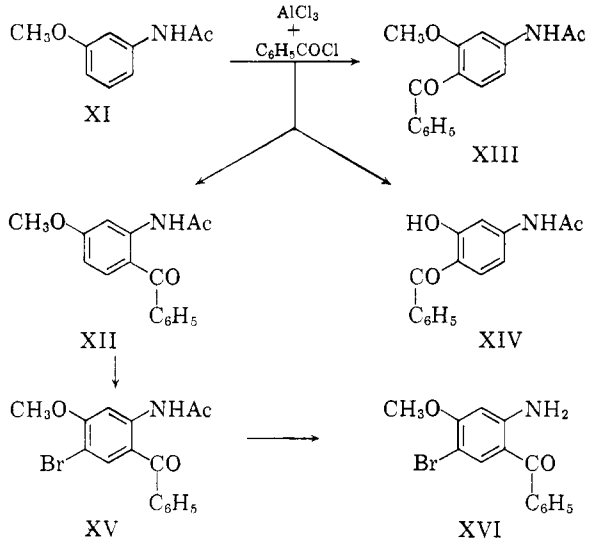
The benzoxazinones (VI) were prepared by condensation of either a substituted anthranilic acid (IV) or the corresponding N-acetanthranilic acid (V) with acetic anhydride. The Grignard reaction afforded the acetamido ketones (VII) in yields generally about 25% but occasionally as high as 50%. In some cases the carbinols (VIII) were also obtained as by-products in low yield. It was generally advantageous to isolate and purify the acetamido ketones (VII), since these intermediates had higher melting points and were easier to crystallize than the corresponding amino ketones (IX). Minor variations in choice of solvent in the Grignard reaction did not appear to affect the yields.

(5) All new *o*-aminobenzophenones and their derivatives are shown in Table I. Compounds with different substituents in the phenyl rings are characterized by different letters following the roman numerals. Identical letters indicate identical substituents.

(6) W. C. Lothrop and P. A. Goodwin, *J. Am. Chem. Soc.*, **65**, 363 (1943).

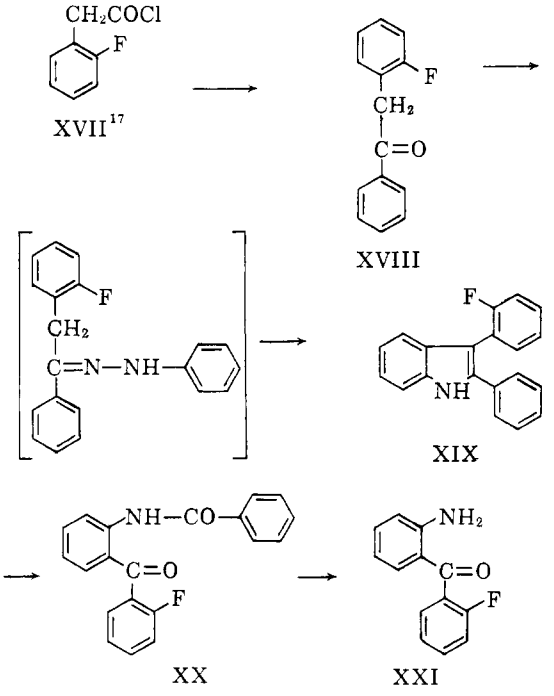
One of the methoxyaminobenzophenones (IXi) prepared by this method was converted into the corresponding phenol (X) by treatment with hydrobromic acid.

The Friedel-Crafts reaction specifically applied to the reaction of *m*-acetanisidine and benzoyl chloride was a third method (C) for the synthesis of *o*-aminobenzophenones. Julia[7] reported that this reaction gave 4-acetamido-2-hydroxybenzophenone (XIV) as the major product. By reducing the proportion of aluminum chloride we were able to isolate three products: 2-acetamido-4-methoxybenzophenone (XII) in 6% yield, 4-acetamido-2-methoxybenzophenone (XIII) in 46% yield, and 4-acetamido-2-hydroxybenzophenone (XIV) in 9% yield. Although the yield of the desired *o*-amino ketone (XII) was low, this method was used since the starting material was readily available.[8] Compound XV was prepared by bromination of XII in acetic acid and yielded on hydrolysis



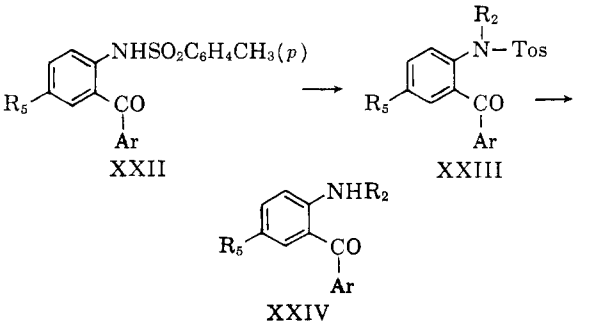
the desired compound XVI (method D). The position of the bromine was not determined, but the course of analogous[10] brominations justified the assumption of the above structure.

The preparation of 2-amino-2′-halobenzophenones by any of the previously described methods was not feasible, since *para*-substitution would occur in a Friedel-Crafts synthesis, and the Grignard reagent (method B), prepared from *o*-dihalobenzene, gave anomalous products *via* a benzyne[11,12] intermediate. Consequently a fourth method of synthesis (method F) was employed, utilizing the well known oxidative fission of the 2,3-double bond of substituted indoles.[13] 2-Phenyl-3-(2-fluorophenyl)indole XIX, prepared by a Fischer synthesis[14] from 2-(2-fluorophenyl)acetophenone XVIII, was ozonized[15,16] to give 2-benzamido-2′-fluorobenzophenone XX which was then hydrolyzed to the required 2-amino-2′-fluorobenzo-



phenone XXI. Although the synthesis appears to be complicated, the yields are excellent, being about 60% overall from *o*-fluorophenylacetyl chloride XVII.

Some of the amino ketones discussed above were characterized as tosyl[18] derivatives and several of them were N-methylated *via* the tosyl-sodio derivatives. The tosyl-sodio derivative XXIIr was



Ar = phenyl or a monosubstituted phenyl
R_2 and R_5 have the same meanings as in the tables

(7) M. Julia, *Bull. soc. chim. France*, 639 (1952).

(8) Lamchen and Wicken[9] prepared 2-amino-4-methoxybenzophenone in 32% yield by the method of Lothrop and Goodwin. However, the preparation of 4-methoxyanthranilic acid involved several steps which made the above procedure preferable.

(9) M. Lamchen and A. J. Wicken, *J. Chem. Soc.*, 2779 (1959).

(10) C. S. Gibson and B. Levin, *ibid.*, 2388 (1931).

(11) G. Wittig, *Ber.*, **91**, 895 (1958).

(12) 2-Amino-4′-fluorobenzophenone has been prepared by a Grignard synthesis [K. Suzuki, E. Weisburger, and J. Weisburger, *J. Org. Chem.*, **26**, 2239 (1961)].

(13) See, for example, K. Schofield and R. S. Theobald, *J. Chem. Soc.*, 796 (1949).

(14) E. Fischer, *Ann.*, **236**, 135 (1886).

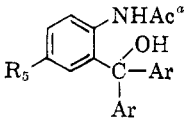
(15) B. Witkop and F. G. Graser, *ibid.*, **556**, 103 (1944).

(16) Several oxidative procedures were tried, including alkaline permanganate, chromic acid, trifluoroperacetic acid, and ozone. Of these only ozone proved in any way successful.

(17) G. A. Olah, A. E. Pavlath, J. A. Olah, and F. Herr, *J. Org. Chem.*, **22**, 879 (1957).

(18) *p*-Toluenesulfonyl.

TABLE II
TRIARYLCARBINOLS

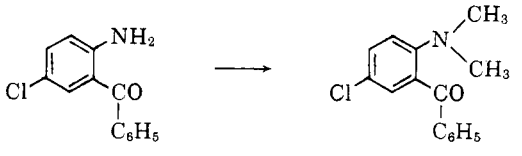


VIII

	R_5	Ar	M.p.	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
i.	CH_3O	C_6H_5	161–162	76.00	6.09	4.03	76.15	6.20	4.13
j.	Cl	$C_6H_4OCH_3(o)$	183–186	67.07	5.38	3.40	67.77	5.50	3.52
	Cl	$C_6H_4OCH_3(m)$[b]	191–193	67.07	5.38	3.40	67.71	5.65	3.55

[a] These carbinols were formed as by-products in method B. They form colorless rods or plates after crystallization from a mixture of benzene and hexane. [b] The corresponding acetamidobenzophenone was not characterized, and was used as a crude oil for the preparation of the bromoacetamidobenzophenone described in the following publication (paper VI).

also converted into the N-ethyl, N-allyl, and N-benzyl derivatives (XXIIIr$_2$-r$_4$). The N-substituted tosylates were hydrolyzed with 70% (v./v.) sulfuric acid to yield the corresponding N-monosubstituted *o*-aminobenzophenones, which were used for the synthesis of benzodiazepinones.[1] Attempts to prepare 2-methylamino-5-chlorobenzophenone by treating XXVr with formaldehyde and formic acid resulted only in the formation of the dimethylamino derivative XXVIr. When the reaction was carried out using smaller amounts of formaldehyde or formic acid, mixtures were obtained which were difficult to separate.



XXVr XXVIr

All new compounds prepared in the course of this work are shown in the following tables (I and II) and are described in the Experimental.

Experimental (with B. Brust and F. Landgraf)

All melting points are corrected. The infrared absorption spectra of starting materials and reaction products were compared wherever necessary in order to establish structural changes. The infrared spectra were determined in 0.3–3% chloroform solutions using a Perkin-Elmer Model 21 spectrophotometer.

5-Substituted 2-Aminobenzophenones (III). Method A.—To 1.125 moles of the benzoyl chloride heated to 120° was added in portions with stirring 0.5 mole of the *para*-substituted aniline. The mixture was then heated to 180–200° and 0.64 mole of zinc chloride was added. The temperature was gradually increased to 200–205° and kept there until the hydrogen chloride evolution had ceased (1–2 hr.). After cooling to 120°, 500 ml. of 3 *N* hydrochloric acid was added cautiously and the mixture stirred and heated to reflux. The hot acid layer was decanted and this procedure repeated two or three times to remove the benzoic acid.

The water-insoluble residue (crude condensation product) was dissolved in 300 ml. of 75% (v./v.) sulfuric acid and refluxed for 40 min. to complete hydrolysis. The hot solution was poured over 1 kg. of ice and diluted with 500 ml. of water. The organic material was extracted with four 300-ml. portions of methylene chloride which were subsequently washed with 500-ml. portions of 3 *N* hydrochloric acid to remove the *para*-substituted aniline and three 500-ml. portions of 5 *N* sodium hydroxide solution to remove the benzoic acid. The methylene chloride extract was dried over anhydrous sodium sulfate, filtered, and the solvent removed to give the crude aminobenzophenone. Recrystallization from methanol gave the pure aminobenzophenone III as yellow crystals.

Method A$_1$.—The condensation was carried out as described under **A** and the crude product hydrolyzed by refluxing for 16 hr. with a mixture of 350 ml. of concentrated hydrochloric acid and 350 ml. of glacial acetic acid. The mixture was concentrated *in vacuo* and worked up as described under **A**.

Method A$_2$.—The condensation was carried out as described under A. The washed crude condensation product was hydrolyzed by refluxing for 24 hr. with 350 ml. of 60% (v./v.) sulfuric acid and then worked up as described under **A**.

Method A$_3$.—The condensation was carried out at 230° and the crude product hydrolyzed by refluxing for 17 hr. with a mixture of 400 ml. of acetic acid and 400 ml. of 48% hydrobromic acid. The mixture was then concentrated *in vacuo* and worked up as described under **A**. The crude aminobenzophenone was distilled at 0.2 mm. and yielded a yellow, viscous oil which did not crystallize. Seeds were obtained from a sample which was purified by vapor chromatography.[19]

Method A$_4$.—The condensation was carried out at 220–230° and the hydrolysis as described under A$_1$. The crude aminobenzophenone was purified by chromatography on a tenfold amount of activated neutral alumina using ether as an eluent.

Method A$_5$.—The condensation was carried out at 220–230°, and the hydrolysis by refluxing for 16 hr. with a mixture of 460 ml. of acetic acid and 230 ml. of concentrated hydrochloric acid. The mixture was concentrated *in vacuo* and worked up as described under **A**. (During the washing with hydrochloric acid, 4-aminodiphenylhydrochloride precipitated and was removed by filtration.) The crude aminobenzophenone was dissolved in a mixture of equal parts of absolute ether and petroleum ether (b.p. 30–60°) and adsorbed on a fifteenfold amount of activated neutral alumina. The product was eluted with a mixture of ether–petroleum ether (4:1).

2-Acetamidobenzophenones (VII), 2-Aminobenzophenones (IX) and Acetamidotriarylcarbinols(VIII). Method B.—A Grignard reagent prepared in the usual manner from 0.25 g.-atom of magnesium and 0.25 mole of an aryl bromide in 40 ml. of ether was added slowly to a stirred

(19) Carried out by Dr. A. Holmgren.

suspension of 0.25 mole of a substituted 2-methyl-4*H*-3,1-benzoxazine-4-one[20] in 500 ml. of dry benzene[21] and 250 ml. of ether cooled to 0–5°. The addition took about 1 hr. The reaction mixture was stirred for 1 hr. in an ice bath and then for 2 hr. at room temperature. It was then cooled in an ice-salt bath, and 250 ml. of 2 *N* hydrochloric acid was cautiously added keeping the temperature below 5°. After the acid was added, stirring was continued for 15 min., the organic layer was separated, washed with water, dilute sodium hydroxide, water, dried over sodium sulfate, and concentrated to dryness *in vacuo*. The residue was crystallized from a mixture of benzene and hexane to give the substituted 2-acetamidobenzophenone. From the mother liquors on fractional crystallization, the acetamidocarbinol (VIII) was obtained in low yield. Unchanged substituted acetylanthranilic acid was recovered by acidification of the alkaline washings. In some instances, the acetamido ketones and carbinols were separated by chromatography on an alumina column using benzene or mixtures of benzene and hexane as eluents. The crude acetamido ketones were sometimes hydrolyzed directly (6 *N* hydrochloric acid and an equal part of alcohol) to the amino ketones and purified at this stage. Several amino ketones were not isolated and the acetamido compounds were used for further synthetic work.[1]

2-Acetamido-4-methoxybenzophenone (XIIo), 4-Acetamido-2-methoxybenzophenone (XIII), and 4-Acetamido-2-hydroxybenzophenone (XIV). Method C.—To a solution of 0.1 mole of *n*-acetanisidine and 0.125 mole of benzoyl chloride in 95 ml. of carbon disulfide, 0.14 mole of anhydrous aluminum chloride was added slowly in portions at 20–25°.[6] After about 10 min. evolution of hydrogen chloride was noted. The reaction mixture was stirred for 1 hr. at 25° and 1 hr. at reflux temperature. The carbon disulfide layer was then decomposed with ice and dilute hydrochloric acid. The mixture was extracted with benzene which was then washed with dilute hydrochloric acid, water, dilute sodium hydroxide (see below for isolation of phenolic material), and finally water. The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvent evaporated *in vacuo* leaving 18.5 g. of a viscous residue. Recrystallization from a mixture of benzene and hexane gave 12.5 g. of 4-acetamido-2-methoxybenzophenone[22] (XIII), m.p. 135–138° (46.5% yield). Further crystallization from a mixture of benzene and hexane raised the melting point to 142–143°.

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.34; H, 5.77; N, 5.11, 5.19.

The benzene–hexane mother liquors from the above crystallizations were concentrated to dryness and the residue crystallized from aqueous ethanol to give 1.7 g. of 2-acetamido-4-methoxybenzophenone (XIIo), m.p. 116–117° (6.4% yield).[23] Further crystallization from dilute ethanol raised the melting point to 118–119.5°. The two isomers (XIII and XIIo) could also be separated by chromatography on alumina, but the yields were not improved.

The sodium hydroxide wash of the original benzene solution was acidified with hydrochloric acid. A crystalline precipitate was obtained (3.5 g.; m.p. 120–140°). On recrystallization from a mixture of benzene and hexane, 2.3 g. of 4-acetamido-2-hydroxybenzophenone (XIV)[24] was isolated, m.p. 152–155° (9% yield). Further crystallization raised the melting point to 153–154° (lit.[7] m.p. 154–155°).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.25; H, 5.32; N, 5.36.

2-Acetamido-5-bromo-4-methoxybenzophenone (XV) and Its Conversion into 2-Amino-5-bromo-4-methoxybenzophenone (XVI). Method D.—A solution of 0.019 mole of 2-acetamido-4-methoxybenzophenone (XII) in 100 ml. of acetic acid was warmed to 50–55° and 0.019 mole of bromine in 25 ml. of glacial acetic acid was added slowly as the bromine was used up. The reaction was kept at 50–55° for 1 hr. after all the bromine had been added. Solvent was then removed by distillation *in vacuo* and the product (XV) recrystallized.

The product (XV) (0.015 mole) was hydrolyzed by refluxing for 3 hr. in 250 ml. of ethanol and 250 ml. of 6 *N* hydrochloric acid. The reaction mixture was concentrated to dryness *in vacuo*, the residue slurried with water, made alkaline with ammonia, and then extracted with benzene. After drying over sodium sulfate, the solvent was removed by distillation *in vacuo*. Crystallization of the residue from a benzene and hexane mixture gave pure 2-amino-5-bromo-4-methoxybenzophenone.

2-Amino-5-hydroxybenzophenone (Xn). Method E.—A solution of 0.023 mole of 2-amino-5-methoxybenzophenone (IXi) in 100 ml. of 48% hydrobromic acid was refluxed for 8 hr. The mixture was then concentrated to dryness *in vacuo*. The residue was dissolved in about 100 ml. of water and the solution carefully neutralized with sodium bicarbonate. The yellow, crystalline precipitate was filtered and recrystallized.

2-Amino-2′-fluorobenzophenone (XXI). Method F.—The preparation of 2-(2-fluorophenyl)acetophenone (XVIII) was essentially that described by Allan and Baker[25] for the synthesis of desoxybenzoin. A mixture of 0.414 mole (63.6 g.) of *o*-fluorophenylacetic acid (XVII)[17] and 1.66 moles (119 ml.) of thionyl chloride was distilled and the last traces removed by codistillation with added benzene (150 ml.). The acid chloride was then diluted with 400 ml. of benzene and transferred to a dropping funnel. The mixture was added with stirring to 0.464 mole (62 g.) of dry aluminum chloride keeping the temperature between 10 and 20° by means of an ice bath. Then the reaction mixture was refluxed for 1 hr. The resultant suspension was poured over a mixture of 500 g. of cracked ice and 170 ml. of concentrated hydrochloric acid. The organic layer was then separated and the aqueous layer extracted with an ether–benzene mixture. The organic layers were combined, washed with water, dried over anhydrous sodium sulfate, and filtered. The solvent was removed under reduced pressure and the residue which solidified on cooling (m.p. 69–72°) was recrystallized from an ether petroleum ether

(20) Two benzoxazinones were new. 5-Chloro-2-methyl-4*H*-3,1-benzoxazin-4-one (VI) was prepared by refluxing 2-carboxy-3-chloroacetanilide [P. Cohn, *Monatsh.*, **22**, 487 (1901)] with a fourfold amount of acetic anhydride for 1 hr. Removal of acetic anhydride by vacuum distillation and crystallization of the residue gave VI in 77% yield. After recrystallization from a mixture of benzene and hexane the product formed crystals melting at 143.5–146°. *Anal.* Calcd. for $C_9H_6ClNO_2$: C, 55.26; H, 3.09; N, 7.16. Found: C, 55.46; H, 3.08; N, 7.25, 7.17. The isomeric 8-chloro-2-methyl-4*H*-3,1-benzoxazin-4-one (VIh) was prepared similarly from 2-carboxy-6-chloroacetanilide in 85% yield. It melted at 131–132° after crystallization from a mixture of benzene and hexane. Found: C, 55.53; H, 3.43; N, 7.21, 7.26. Permanganate oxidation of 2-methyl-6-chloroacetanilide gave 2-carboxy-6-chloroacetanilide melting at 206–208° after crystallization from acetonitrile. It was prepared by Mr. L. A. Dolan. *Anal.* Calcd. for $C_9H_8ClNO_3$: C, 50.60; H, 3.78; N, 6.56. Found: C, 50.69; H, 4.10; N, 6.37, 6.41.

(21) In the experiment leading to IX, methylene chloride was used as solvent with little effect on the yield.

(22) The structure of 4-acetamido-2-methoxybenzophenone XIII was established by its conversion to 4-amino-2-hydroxybenzophenone, m.p. 127–128° (reported[7] 125°), by refluxing with 48% hydrobromic acid.

(23) Mentioned but not isolated by Lamchen and Wicken.[9]

(24) The structure of this compound (XIV) was confirmed by hydrolysis to 4-amino-2-hydroxybenzophenone identical with the compound obtained from XIII.[22]

(25) C. F. H. Allen and W. E. Barker, *Org. Syntheses*, **12**, 156 (1932).

(b.p. 30–40°) mixture to give 89 g. (an almost quantitative yield) of 2-(2-fluorophenyl)acetophenone (XVIII) as colorless plates melting at 75–75.5°.

Anal. Calcd. for $C_{14}H_{11}FO$: C, 78.49; H, 5.18; Found: C, 78.46; H, 4.95.

A mixture of 0.41 mole of XVIII and 0.42 mole of phenylhydrazine was heated on the steam bath for 4 hr. The crude phenylhydrazone was cyclized by refluxing the oil obtained above in a mixture of 500 ml. of concentrated hydrochloric acid and 750 ml. of methanol for 45 hr. Methanol was removed under reduced pressure and the hydrochloric acid was decanted from the oil thus formed. This residue was taken up in 600 ml. of methylene chloride and washed with an excess of dilute ammonia. The methylene chloride layer was then washed alkali free with water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was crystallized from ligroin (b.p. 90–120°) to give 88 g. (75% yield) of 2-phenyl-3-(2-fluorophenyl)indole XIX forming colorless needles, melting at 132–132.5°.

Anal. Calcd. for $C_{20}H_{14}FN$: C, 83.60; H, 4.91. Found: C, 83.48; H, 4.73.

A solution of 1 g. of the indole in 5 ml. of glacial acetic acid was ozonized to completion,[14] diluted with 10 ml. of water, and evaporated to dryness at 85° under reduced pressure. The residue was partitioned between water and methylene chloride. The organic layer was treated with decolorizing charcoal, dried over anhydrous sodium sulfate, and filtered. Removal of the solvent gave 1.0 g. of an oil which solidified on cooling (m.p. 110–113°). Recrystallization from hexane gave 930 mg. of pure 2-benzamido-2′-fluorobenzophenone (XX).

Hydrolysis was achieved by refluxing for 16 hr. a solution of 0.01 mole (3.2 g.) of XX in a mixture of 44 ml. of sulfuric acid, 23 ml. of water and 33 ml. of acetic acid. The reaction mixture was cooled, diluted with 100 ml. of water and extracted with methylene chloride. The methylene chloride solution was washed with a saturated brine solution, dried over anhydrous sodium sulfate, filtered and concentrated. The residual oil was extracted with several portions of boiling hexane and the combined hexane extracts were concentrated and cooled. The 2-amino-2′-fluorobenzophenone (XXI) crystallized and was isolated by filtration.

2-Tosylamidobenzophenones (XXII). Method G.—A solution of 1 mole of the *o*-aminobenzophenone, and 1.2 moles of *p*-toluenesulfonyl chloride in 1000 ml. of pyridine was refluxed for 90 min. Part of the pyridine (500 ml.) was then distilled and the residue poured into 2.5 l. of water and stirred until the oil had solidified (*ca.* 30 min.). The precipitate was filtered, washed with hot water followed by petroleum ether (b.p. 30–40°), and recrystallized.

Sodium salt of 2-tosylamido-5-chlorobenzophenone (XXIIIr). Method G_1.—To a solution of 1 mole of the crude tosyl derivative XXIIr in 600 ml. of boiling benzene, 150 ml. of a 40% sodium hydroxide solution was added. The mixture was stirred and refluxed for 1 hr. The suspension of the sodium salt was then cooled to 25° and filtered. The precipitate was washed with hot benzene and water, dried, and recrystallized from a dilute of dimethylformamide and chloroform.

N-Substituted 2-Tosylamidobenzophenones (XXIII). Method H.—A mixture of 0.01 mole of the tosylamidobenzophenone, 25 ml. of toluene, and a solution of 0.01 mole of sodium methoxide[26] in 2.5 ml. of methanol was stirred at room temperature for 30 min. Dimethyl sulfate (0.02 mole) was then added and the stirring continued for a further 2 hr. (room temperature). Excess dimethyl sulfate was destroyed by stirring for an additional 10 min. with 25 ml. of 3 *N* sodium hydroxide. Water was added and the product extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was crystallized from ethanol.

Method H_1.—The tosylamidobenzophenone (0.09 mole) (XXII) was dissolved in 100 ml. of a 1 *N* methanolic sodium methoxide solution and a sufficient amount of methanol to produce a clear solution. The methanol was removed *in vacuo* and the residue dissolved in 250 ml. of dimethylformamide. On addition of 30 ml. of methyl iodide the temperature of the solution rose to 30°. The mixture was kept at room temperature for 1 hr., then most of the solvent was removed *in vacuo* and the residue poured into water. The precipitated crystals were separated by filtration and recrystallized.

Method H_2.—A solution of 0.024 g. atom of sodium in about 50 ml. of methanol was added to a solution of 0.02 mole of the dry tosylamidobenzophenone in 75 ml. of toluene and the mixture refluxed and stirred for 90 min. Methanol and a small part of the toluene were distilled and to the precipitated sodio derivative dimethyl or diethyl sulfate (0.04 mole) was added. The mixture was stirred and refluxed for 1 hr., then excess alkyl sulfate was destroyed by refluxing for 1 hr. with 50 ml. of 3 *N* sodium hydroxide. The reaction mixture was cooled and the toluene solution separated, dried, and concentrated *in vacuo*. The pale yellow residue was used as such in the next step or was purified by recrystallization.

Method H_3.—A suspension of 0.02 mole of the sodio derivative of 2-tosylamido-5-chlorobenzophenone in 60 ml. of anhydrous acetonitrile was refluxed for 90 min. with 0.04 mole of allyl bromide. Sodium bromide was removed by filtration, the solution concentrated, and the oily residue detosylated as described under J_2.

Method H_4.—The reaction was carried out as described under H_3 using for the alkylation 0.12 mole of benzyl chloride with the addition of 0.002 mole of sodium iodide. The oily residue obtained after filtration was dissolved in ether, which was then washed with water, dried, and partly concentrated to yield the crystalline reaction product.

Detosylation to N-substituted 2-Aminobenzophenones (XXIV). Method J.—Into 200 ml. of 70% (v./v.) sulfuric acid preheated to 105°, 10 g. of the substituted tosylamidobenzophenone was introduced. The mixture was stirred and heated to 145° until a clear solution resulted (approximately 8 min.) and then poured over 1 kg. of crushed ice. The yellow reaction product was filtered off, washed thoroughly with water, and crystallized.

Method J_1.—Compound XXIIIs (0.1 mole) was refluxed for 20 hr. with 500 ml. of a mixture prepared by combining 325 ml. of concentrated sulfuric acid, 250 ml. of acetic acid, and 75 g. of ice. The solution was poured over ice, and the product extracted with ether. The ether layer was washed neutral with 2 *N* sodium hydroxide, concentrated, and the residue was crystallized.

Method J_2.—The crude oily tosylation product (*ca.* 0.01 mole, methods H_2 and H_3) was dissolved in 10 ml. of glacial acetic acid and was added to 70 ml. of 70% (v./v.) sulfuric acid at 105°. The mixture was stirred and heated to 145° within 8 min. The resulting dark, clear solution was poured over 500 g. of crushed ice and the product extracted with ether. The ether layer was washed with 1 *N* sodium hydroxide, dried, concentrated *in vacuo*, and the residue crystallized from methanol to give yellow needles or prisms.

2-Dimethylamino-5-chlorobenzophenone (XXVIr). Method K.—A solution of 0.05 mole of 2-amino-5-chlorobenzophenone in a mixture of 23 ml. of formic acid and 14 ml. of 40% aqueous formaldehyde was refluxed for 14 hr. The mixture was diluted with water and extracted with ether. The ether solution was washed with 3 *N* sodium hydroxide and water and concentrated *in vacuo*. The residue was crystallized and gave melting point depressions

(26) If the sodium methoxide were omitted, the yield was considerably lower (*ca.* 20%).

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

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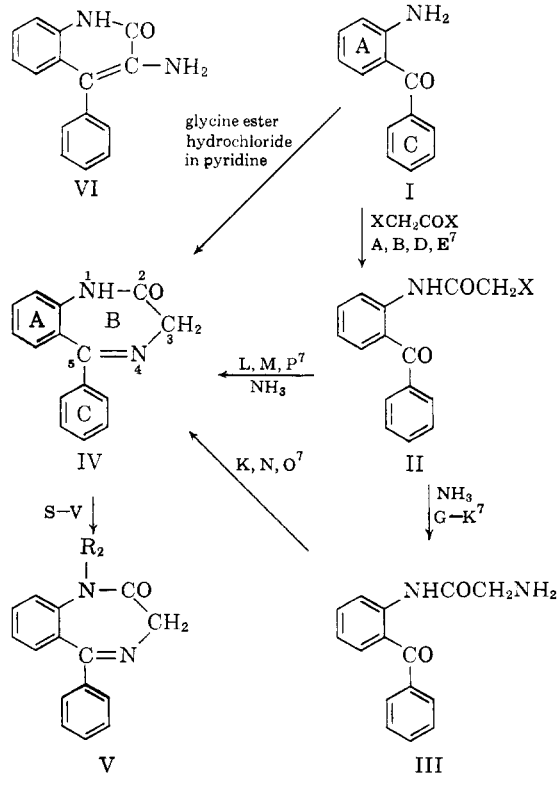
Two new methods for the synthesis of 1,4-benzodiazepin-2-ones are reported. A number of new 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones, and intermediates leading to these compounds, are described.

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.