Quinazolines and 1,4-Benzodiazepines. XXXIV.[1] 4,1,5-Benzoxadiazocin-2-ones,[2] a Novel Ring System

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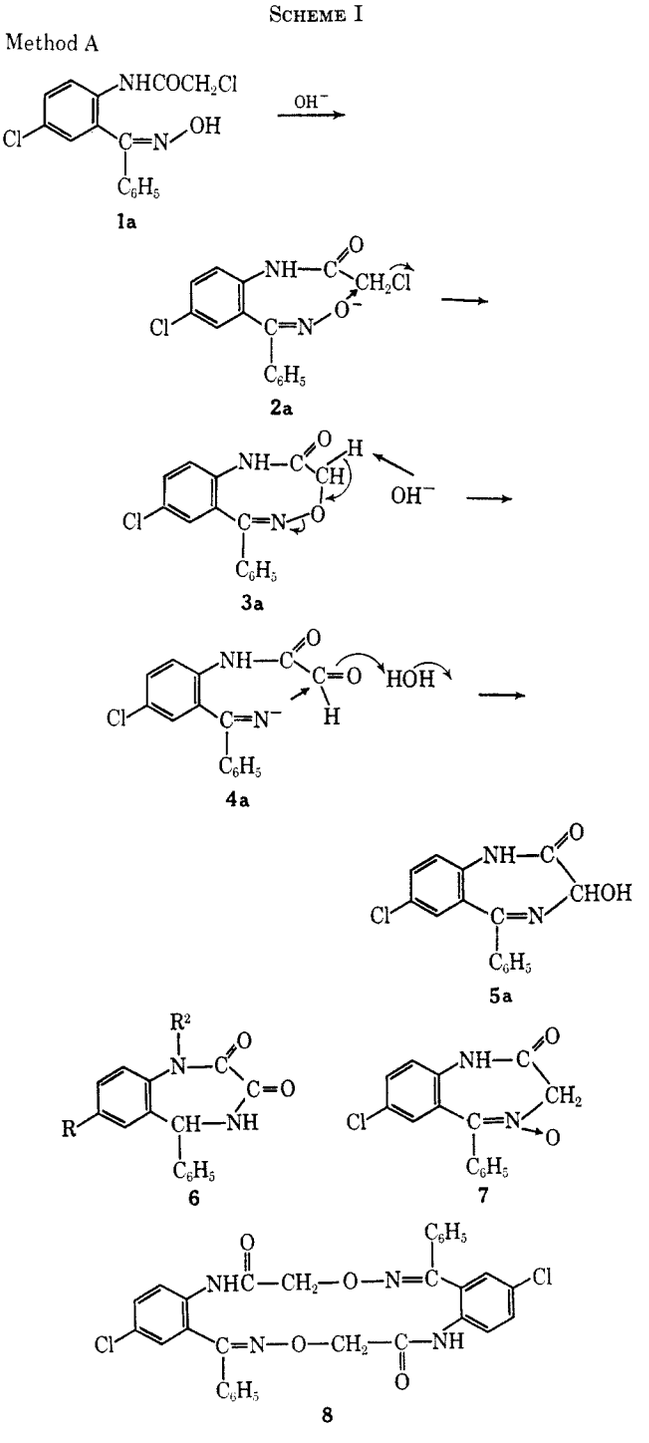
In an alkaline medium, *o*-haloacetamidobenzophenone *syn*-oximes undergo intramolecular O-alkylation with the formation of 4,1,5-benzoxadiazocin-2-ones. These compounds, in most cases, readily rearrange with alkali to form 3-hydroxy-1,4-benzodiazepin-2-ones. The 4,1,5-benzoxadiazocin-2-one ring system has been synthesized by several unequivocal routes.

The formation of 1,4-benzodiazepin-2-one 4-oxides of type **7** by treatment of *o*-haloacetamidobenzophenone *anti*-oximes with dilute alkali under mild conditions has been reported by Sternbach and co-workers.[3,4] This intramolecular alkylation of the oxime gave only one product, the result of N-alkylation, which was formed in very high yield. Since alkylation of benzophenone oximes has been generally reported to result in mixtures of N- and O-alkylated products,[5,6] it was of interest for us to investigate the reactions of the readily available *syn*-oximes[7] of type **1**.

When reaction conditions were employed under which the *anti*-oxime **1a** (Scheme I) gave an almost quantitative yield of **7** (1 equiv of alkali at room temperature), the corresponding *syn* isomer gave a more complex mixture of products. The major product was an extremely insoluble "dimer" (**8**), of the same empirical formula as **5a** and **7**, whose probable structure will be discussed below. From the mother liquors, a small amount of 1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one (**5a**)[8] was isolated. When this reaction was repeated using 2 equiv or more of alkali, the yield of the "dimer" (**8**) became very small and the major product, isolated in yields approaching 60%, was **5a**. Further treatment of **8** with alkali under the same mild conditions left the material unchanged and did not produce compound **5a**. It would,

SCHEME I



(1) Paper XXXIII: G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Am. Chem. Soc.*, **89**, 332 (1967).

(2) K. v. Auwers and E. Freese [*Ann. Chem.*, **450**, 273 (1926)] reported the synthesis of 4,1,5-benzoxadiazocin-2-one by treatment of 2-chloroacetamidobenzaldehyde oxime with alkali. Our studies, to be submitted for publication, showed that this compound does not have the structure described in the literature.

(3) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).

(4) A. Stempel, E. Reeder, and L. H. Sternbach, *ibid.*, **30**, 4267 (1965).

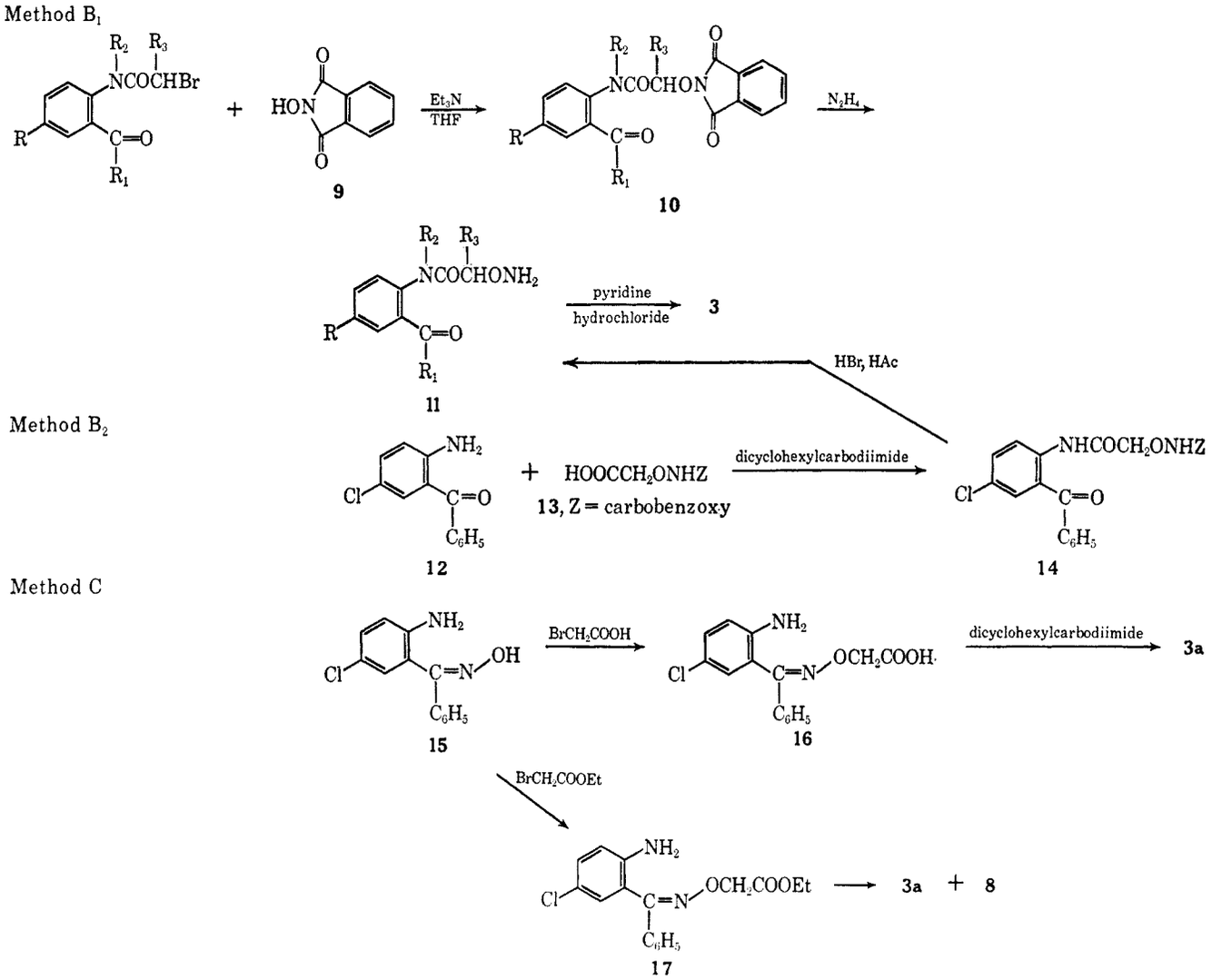
(5) P. A. S. Smith and J. E. Robertson, *J. Am. Chem. Soc.*, **84**, 1197 (1962).

(6) J. Hamer and A. Macaluso, *Chem. Rev.*, **64**, 473 (1964).

(7) The terms *syn* and *anti* are used as defined by (a) L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Am. Chem. Soc.*, **82**, 475 (1960), footnote 9. In the *syn* isomer, the oxime hydroxyl is *syn* to the amino-substituted phenyl group. The structural assignments in **7a** were based on a comparison of infrared spectra of the oximes with those of the pair of known 2-aminobenzophenone oximes whose structure had been determined by classical chemical transformations; see (b) F. v. Meyenburg, *Ber.*, **26**, 1657 (1893), and (c) J. Meisenheimer, O. Senn, and P. Zimmerman, *Ber.*, **60**, 1736 (1927). In addition to the infrared spectra in 1–5% solution discussed in 7a, the spectra in high dilution (0.2% chloroform) were also studied. The strong intermolecular hydrogen bonding characteristic of the *syn*-oximes in concentrated solution disappeared on dilution, but the *anti*-oxime now exhibited intramolecular hydrogen bonding owing to the formation of a six-membered ring. This was evidenced by the symmetric NH vibration of the *anti*-oxime at or about 70 cm^{-1} higher wave length than that observed for the *syn*-oxime. The infrared spectra have been discussed by (d) J. G. Pritchard, G. F. Field, K. Koch, G. Raymond, L. H. Sternbach, V. Toome, and S. Traiman [*Appl. Spectry.*, **20**, 363 (1966)] who also reported characteristic differences in the nmr and ultraviolet spectra of pairs of oximes. Further, they found that *anti*-oximes in the series studied formed colored complexes with Cu^{2+} while the *syn* isomers did not. Additional corroborative chemical evidence for the structure of these oximes was obtained by (e) T. S. Sulkowski and S. J. Childress [*J. Org. Chem.*, **27**, 4424 (1962)] by reaction of a pair of 2-aminobenzophenone oximes with phosgene and by (f) G. F. Field, W. J. Zally, and L. H. Sternbach [*ibid.*, **30**, 3957 (1965)] who found that only *anti*-oximes of 2-aminobenzophenones cyclized on reaction with aldehydes and ketones to 1,2-dihydroquinazoline 3-oxides.

(8) S. C. Bell and S. J. Childress, *ibid.*, **27**, 1691 (1962).

SCHEME II



therefore, appear that **8** is not an intermediate in the formation of **5a**. We have no explanation as yet for the high yields of **8** which can be obtained under certain conditions. However, the formation of both products (**5a** and **8**) can best be explained by a series of reactions that proceed *via* the mechanism outlined in Scheme I.[9]

In the alkaline medium, the anion of the oxime (**2a**) formed at first displaces the leaving group to form a C–O bond. This step could be intramolecular to form **3a** or intermolecular to form a "dimer" such as **8** or a higher polymer. Further attack of hydroxyl ion on compound **3a** then removes one of the activated hydrogens at C-3 leading to the formation of **4a**. The anion of the imine (**4a**) would then add to the aldehyde carbonyl yielding compound **5a**.[10] An additional transformation of **5a** may occur in some cases which results in the formation of a compound of type **6**.[8]

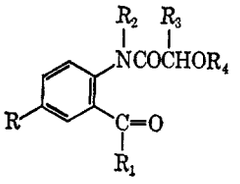
A closer study of the reaction revealed facts which were in good agreement with this postulated mechanism. As mentioned before, compound **1a** on treatment with at least 2 equiv of alkali yielded **5a** after a short time. This was, however, preceded by the formation of another compound as could be established by thin layer chromatography. When the reaction was interrupted after a brief period, this compound, 8-chloro-1,3-dihydro-6-phenyl-2H-4,1,5-benzoxadiazocin-2-one (**3a**), an isomer of **5a**, could be isolated. Physicochemical data and additional chemical studies which will be discussed below established the identity of **3a** beyond any doubt. In alkaline solution, **3a** rearranged rapidly to **5a**, proof that it was indeed an intermediate. These reactions show that, whereas treatment of the *anti* isomer of **1a** with alkali resulted in N-alkylation[3] exclusively, the *syn*-oxime **1a** under identical conditions gave only **3a** and **8**, both products of O-alkylation. It is, therefore, evident that in the intramolecular alkylation of oximes in this series the steric configuration of the oxime determines the site of attack.

In order to obtain additional proof for structure **3a**, this compound was prepared by several unequivocal methods as outlined in Scheme II. The new ring system could be built up by suitable acylation of an *o*-aminobenzophenone (methods B_1 and B_2) or by O-alkylation of the corresponding *syn*-oxime (method C) followed in both cases by cyclization of the intermediates.

(9) We are greatly indebted to Dr. G. Field who suggested this mechanism.

(10) A similar mechanism has been proposed for the rearrangement of a 1,2-diazepin-4-one to an α-aminopyridine: J. A. Moore and E. C. Zoll, *J. Org. Chem.*, **29**, 2124 (1964).

TABLE I

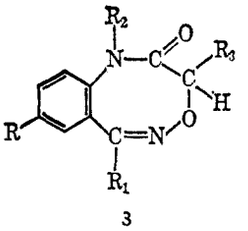


10 and 11

Compd	R	R_1	R_2	R_3	R_4	Mp, °C	Crystd from[a]	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
10a	Cl	C_6H_5	H	H	Phth[b]	183–185	EtOAc	82	63.53	3.48	6.44	63.77	3.73	6.43
14	Cl	C_6H_5	H	H	NHZ[c]	115–116	b + h	38	62.95	4.36	6.38	62.96	4.04	6.25
11a	Cl	C_6H_5	H	H	NH_2	85–87	b + h	97	59.12	4.30		59.33	4.34	
10b[d]	H	C_6H_5	H	H	Phth	174–176	b	83	68.99	4.03	7.00	69.23	4.19	6.82
10c	Cl	C_6H_5	CH_3	H	Phth	164–166	EtOAc	85	64.22	3.82	6.24	64.30	4.06	6.26
10d	NO_2	C_6H_5	H	H	Phth	203–204	EtOAc	52	62.02	3.39	9.44	62.20	3.39	9.58
11d	NO_2	C_6H_5	H	H	NH_2	141–143	b + h	95	57.14	4.16		57.26	4.38	
10e	CF_3	C_6H_5	H	H	Phth	191–193	EtOAc	73	61.54	3.23	5.98	61.82	3.13	5.96
11e	CF_3	C_6H_5	H	H	NH_2	79–81	h	95	56.81	3.87	8.28	56.68	3.75	8.06
10f	Br	2-Pyridyl	H	H	Phth	199–201	b	77	55.02	2.94		54.83	3.08	
10g	Cl	C_6H_5	H	CH_3	Phth	183–186	EtOAc	35	64.22	3.82	6.24	64.04	3.79	6.27
11g	Cl	C_6H_5	H	CH_3	NH_2	104–106	EtOH	82	60.29	4.74	8.79	60.51	4.63	9.02
10n	H	CH_3	H	H	Phth	185–186	ch + h	78	63.90	4.17	8.28	64.07	3.91	8.32
11n	H	CH_3	H	H	NH_2	105–106	mc + h	62	57.68	5.81	13.46	57.50	5.68	13.25

[a] b = benzene, h = hexane, ch = chloroform, mc = methylene chloride. [b] Phth = phthalimido. [c] Z = carbobenzoxy. [d] Compound **11b** was not obtained in the crystalline form.

TABLE II



3

Compd	R	R_1	R_2	R_3	Method	Mp, °C	Crystd from[a]	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
a	Cl	C_6H_5	H	H	B	198–199	b	34	62.84	3.87	9.77	62.96	3.71	9.80
b	H	C_6H_5	H	H	B	236–238	b	34	71.41	4.80	11.11	71.13	4.97	10.82
c	Cl	C_6H_5	CH_3	H	D	130–132	h	12	63.90	4.36	9.32	63.61	4.57	9.46
d	NO_2	C_6H_5	H	H	B	253–255	mc + h	4	60.60	3.73	14.14	60.34	3.52	13.95
e	CF_3	C_6H_5	H	H	B	212–214	mc + h	9	60.00	3.46	8.76	60.21	3.26	8.85
f	Br	2-Pyridyl	H	H	A	229–231	THF + h	30	50.62	3.03	12.65	50.87	3.20	12.45
g	Cl	C_6H_5	H	CH_3	B	170–172	mc + h	51	63.90	4.36	9.32	64.06	4.18	9.30
h	H	CH_3	H	H	B	216–217	b	30	63.15	5.30	14.73	63.11	5.14	15.04

[a] b = benzene, h = hexane, mc = methylene chloride.

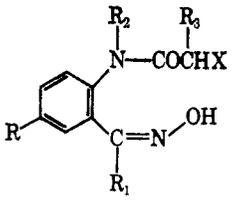
Method B_1 proved to be of widest utility for the synthesis of the 4,1,5-benzoxadiazocine ring system. The reaction of an *o*-haloacetamidophenyl ketone with **9** gave a high yield of **10a** (Table I). Removal of the protective phthaloyl group by hydrazinolysis resulted in an almost quantitative conversion to **11a**. Cyclication to the desired benzoxadiazocine (**3a**) occurred in refluxing pyridine containing pyridine hydrochloride in 34% yield. The major by-product appeared to be a polymer which was not identical with the compound to which the structure **8** is ascribed.

In an alternate synthesis (B_2) of the eight-membered ring system (**3**), aminoxyacetic acid in which the amino group was protected by a carbobenzoxy group (**13**) was used. Formation of the amide **14** from **12** and **13** in the presence of dicyclohexylcarbodiimide gave only a 38% yield; therefore method B_1 was preferable.

In another synthetic route (method C), alkylation of the *syn*-oxime **15** with bromoacetic acid gave **16** in good yield. Mass spectroscopy indicated that **16** had the structure shown and was not the isomeric nitrone produced by N-alkylation. There was no peak at *m/e* 288 (M − 16) owing to loss of oxygen which would be expected of nitrones, but there was a strong peak at *m/e* 229 (M − 75) indicating loss of OCH_2COOH. Cyclization of **16** under mild conditions with dicyclohexylcarbodiimide gave **3a** in about a 20% yield. The corresponding ethyl ester (**17**), prepared in a similar manner, proved to be very difficult to cyclize to **3a**. Only a small amount of **3a** could be isolated when **17** was heated in refluxing xylene containing *p*-toluenesulfonic acid. The reaction yielded predominately a mixture of undefined polymers containing a small amount of compound **8**.

The syntheses of the benzoxadiazocines shown in Scheme II are unequivocal and prove that the primary reaction product formed on treatment of **1a** with alkali has the structure **3a**. Differentiation of **3a** from the three possible isomers **5a**, **6a**, and **7a** was most readily achieved by a comparison of the nmr spectra. These

TABLE III



1

Compd	R	R_1	R_2	R_3	X	Mp, °C	Crystd from[a]	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
a[b]	Cl	C_6H_5	H	H	Cl	...[c]								
b	H	C_6H_5	H	H	Cl	136–137	mc + h	83	62.40	4.54	9.70	62.09	4.71	9.72
c	Cl	C_6H_5	CH_3	H	Cl	171–178	mc + h	63	56.99	4.18		56.89	4.08	
d	NO_2	C_6H_5	H	H	Cl	199–200	THF + h	53	53.98	3.62	12.59	54.07	3.79	12.70
e	CF_3	C_6H_5	H	H	Cl	174–176	b	72	53.87	3.39	7.85	53.83	3.34	7.95
f[d]	Br	2-Pyridyl	H	H	Cl	166–168	EtOH	65	45.61	3.01	11.40	45.67	3.16	10.91
g	Cl	C_6H_5	H	CH_3	Br	145–146	b	83	50.35	3.70		50.71	3.67	
h	Cl	C_6H_5	H	H	Br	148–149	e + h	80	49.03	3.29	7.62	48.82	3.16	6.95
i	Cl	C_6H_5	H	H	I	146–148	mc + h	81	43.45	2.92		43.57	2.95	
j	Cl	C_6H_5	H	H	Tosyl	159–160	b	80	57.58	4.17	6.10	57.28	4.25	6.06
k	Cl	C_6H_5	H	H	Mesyl	136–138	mc + h	79	50.20	3.95	7.32	50.33	3.95	7.22
l	Cl	C_6H_4OH-*p*	H	H	Cl	169–170	CH_3CN	79	53.12	3.57		53.04	3.51	
m	Cl	C_6H_5	H	H	OCH_3	155–157	b	15	60.27[e]	4.75	8.80	60.10	4.70	8.75

[a] b = benzene, h = hexane, EtOH = ethanol, e = ether, mc = methylene chloride, THF = tetrahydrofuran, ch = chloroform. [b] The lower case letters following an arabic numeral in the text and tables always refer to the same substituents. [c] Footnote 7. [d] First prepared by R. Schmidt. [e] *Anal.* Calcd: OCH_3, 9.74. Found: OCH_3, 9.41.

spectra were particularly valuable in assigning structures in cases in which all of the isomers were not available. The spectrum of compound **3a** showed a very characteristic AB pattern centered at δ 4.85 (J = 16.5 cps) produced by the two protons on C-3. In marked contrast, these two protons in **7** appear as a singlet at δ 4.62 and it is obvious that in **5a** there is only one proton at C-3 which appears as a singlet at δ 5.03. The splitting of the peaks of the two protons at C-3 in **3a** which was not observed in compounds of structure **7** indicates that conformers of the seven-membered ring system interconvert rapidly at room temperature. In the benzoxadiazocine ring (**3**), interconversion is much slower and splitting of the peaks of these two protons is observed. This splitting pattern was characteristic of all the benzoxadiazocines shown in Table II with the exception of **3g**. In compound **3g**, the CH_3 protons appeared as a doublet centered at δ 1.45 (J = 7 cps) and the proton on C-3 produced a quartet centered at δ 4.97 (J = 7 cps).

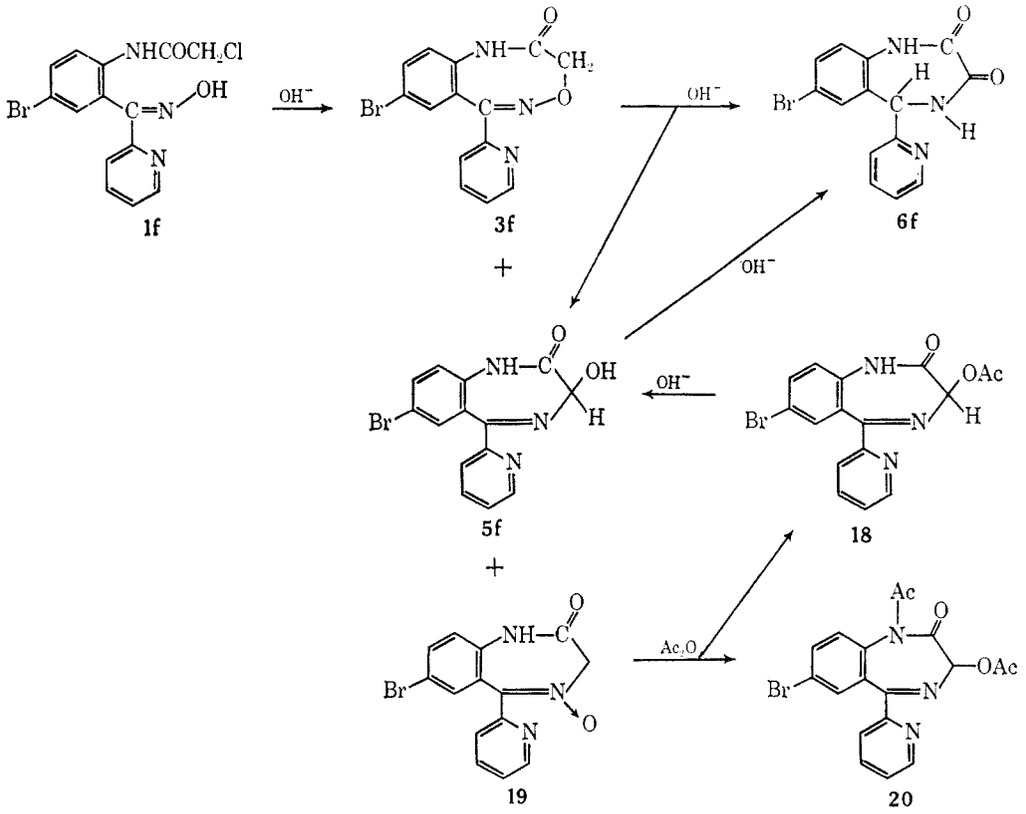
The mass spectra of **3a** and **7** exhibited very characteristic differences. Compound **3a** showed a very strong peak at m/e 228 (M − 58) ascribed to loss of $COCH_2O$ which was not found in the spectrum of **7**. The nitrone (**7**), as expected, had a strong peak at m/e 270 (M − 16) owing to loss of oxygen but none at m/e 228.

The synthetic routes leading to 4,1,5-benzoxadiazocin-2-ones shown in Schemes I and II (methods A and B) proved to be quite general. With one exception (**3c**), the compounds listed in Table II were prepared employing these approaches. While method A was not particularly suitable for the preparation of large amounts of **3a**, it was a convenient approach for preparing some closely related compounds. The rate of synthesis of 4,1,5-benzoxadiazocin-2-ones (**3**) from **1** and the subsequent rearrangement to the corresponding 3-hydroxy-1,4-benzodiazepin-2-ones (**5**) appeared to be influenced by many factors. Changes in the substitution of **1** markedly affected the proportions of the products obtained. When **1d** (R = NO_2, R_1 = C_6H_5, Table III), was treated with alkali, using conditions under which **1a** gave only **5a**, both **3d** and **5d** were isolated, although in low yield. Similar results were obtained employing **1f** (R = Br, R_1 = 2-pyridyl) as starting material. In this case, reaction with alkali gave three products (Scheme III), a 30% yield of **3f**, a 10% yield of **5f**, and a 1.5% yield of 7-bromo-1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one 4-oxide (**19**). The latter compound was probably formed from a small amount of the *anti*-oxime present as a contaminant in the sample of **1f**. Compound **5f** was also prepared by a Polonovski rearrangement of **19** (**19** → **18** → **5f**). Heating **19** with acetic anhydride resulted in a mixture of monoacetyl (**18**) and diacetyl (**20**) derivatives. On alkaline hydrolysis, **18** gave a mixture of **5f** and **6f** in which the dicarbonyl compound **6f** generally was the predominant product. The process starting with **1f** was clearly superior for the synthesis of **5f**, particularly since **3f** on further treatment with alkali rearranged to **5f** in 33% yield and gave only traces of **6f**.

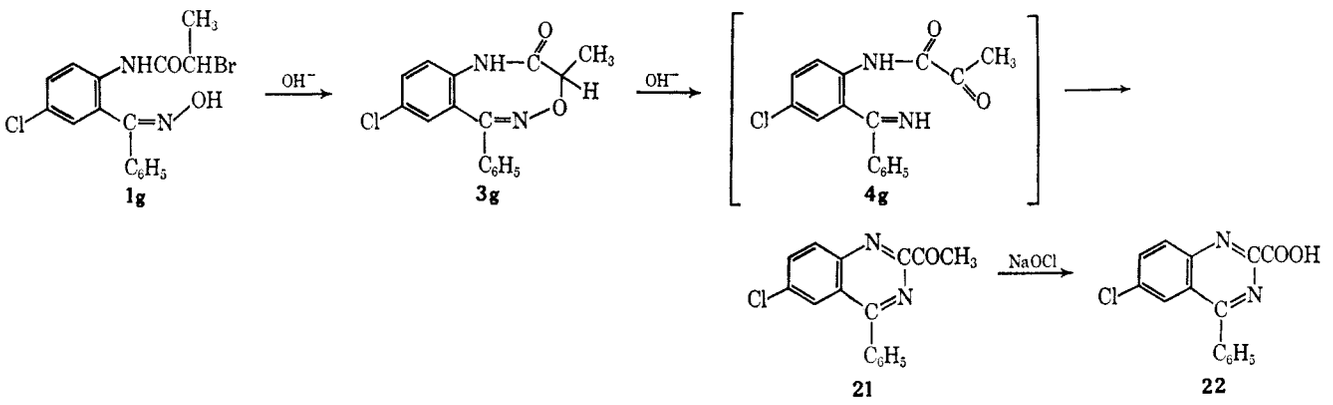
Compound **3f** was not prepared by method B_1 since the phthaloyl group of the intermediate **10f** did not cleave under the usual mild conditions of hydrazinolysis. Similar difficulties were experienced in removing the protective group of **10c** (Table I).

Substitution of a methyl group in position 3 of the benzoxadiazocine ring (**3g**, Scheme IV) greatly decreased the rate at which the ring rearranged in the presence of alkali. Because of this increased stability, **3g** could be prepared from **1g** in 87% yield. On further treatment with alkali, **3g** rearranged to 2-acetyl-6-chloro-4-phenylquinazoline (**21**) rather than to the expected 3-hydroxy-1,4-benzodiazepin-2-one. The isolation of **21** is in good agreement with our postulate

SCHEME III



SCHEME IV



that a species such as **4g** is the result of reaction of **3g** with alkali.[11] Although the formation of **5** from **4** (Scheme I) would usually be favored, the presence of a methyl group next to the carbonyl (**4g**) may cause steric hinderance or reduce the positive charge on the ketone carbon so that reaction takes place on the amide carbonyl group resulting in the quinazoline **21**. The structure of **21** was proved by mild oxidation to **22**.[12]

A further effect of substitution was observed when **1c** (Table III, alkylated amide nitrogen) was treated with sodium methoxide in methanol. A mixture of **5c** and **6c**[8] was obtained. When the reaction was carried out in dioxane and aqueous sodium hydroxide, predominantly **6c** was formed. In general, it was found that the rate of reaction was slower when sodium methoxide in methanol was employed. Aqueous sodium hydroxide in dioxane possessed a further advantage in many cases since the sodium salt of **5** crystallized from the reaction mixture. The use of 40% sodium hydroxide, in large excess, in methanol resulted in nucleophilic displacement of the halide in **1a** with the formation of **1m** in addition to O-alkylation and rearrangement to **5a**. Method A is of general utility for the preparation of compounds of type **5** and **6** and has been carried out successfully with compounds **1a–l**.

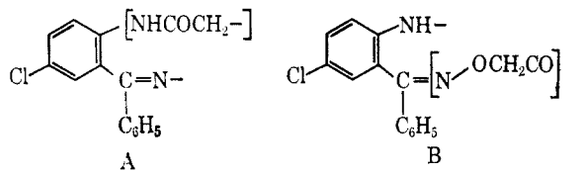
N-alkylation of the 1-position of 4,1,5-benzoxadiazocin-2-ones (**3**) could be carried out in the same manner as that used for the 1,4-benzodiazepin-2-ones.[3] The yield obtained in one experiment was surprisingly low (method D, Table II). On rearrangement of **3c** with aqueous alkali in ethanol, a good yield of 7-chloro-1-methyl-5-phenyl-4,5-dihydro-2H-1,4-benzodiazepin-2,3-dione (**6c**)[8] was obtained.

Compound **8** has not been studied extensively and the structure proposed is based on the following evidence. Mass spectroscopy showed a molecular ion

(11) A similar intermediate has been proposed in the rearrangement of **5a** to 6-chloro-4-phenylquinazoline-2-carboxaldehyde with acid: S. C. Bell and S. J. Childress, *J. Org. Chem.*, **29**, 506 (1964).

(12) L. H. Sternbach, E. Reeder, A. Stempel, and A. I. Rachlin, *ibid.*, **29**, 332 (1964).

at m/e 572 and no peaks were visible above 572. Since **8** was prepared from both **1a** and **17**, the structures A and B must both be contained in the product. The structure **8** would satisfy all of these conditions.



A B

Experimental Section[13]

2-Amino-5-chloro-4′-hydroxybenzophenone *syn*-Oxime.—A solution of 10 g (40 mmoles) of 2-amino-5-chloro-4′-hydroxybenzophenone[14] and 5.6 g (80 mmoles) of hydroxylamine hydrochloride in a mixture of 55 ml of ethanol and 7 ml of pyridine was stirred and refluxed for 20 hr. Solvent was removed by distillation under reduced pressure and the residue was partitioned between water and ether. The organic phase was washed with water, dried over anhydrous sodium sulfate, and concentrated to dryness. Warming the residue with benzene gave 7.4 g of crystalline oxime, mp 151–153°, 70% yield. Recrystallization from a mixture of ethyl acetate and hexane gave colorless rhombs: mp 151–153°; infrared (KBr disk) absorption at 3400, 3330, 1605, 1590, 1515, 1485 cm^{-1}. Assignment of configuration was based on chemical transformation of **11** to **5l** on treatment with alkali since the usual methods of assignment, infrared, ultraviolet, and nmr were not unequivocal in this instance.

Anal. Calcd for $C_{13}H_{11}ClN_2O_2$: C, 59.44; H, 4.22; N, 10.66. Found: C, 59.66; H, 4.54; N, 10.07.

2,4′-Dichloro-2′-(4-hydroxybenzoyl)acetanilide *syn*-Oxime (11).—A solution of 16.1 g (61 mmoles) of 2-amino-5-chloro-4′-hydroxybenzophenone *syn*-oxime in 500 ml of ether was stirred with 200 ml of water and cooled in an ice bath to 0–5°. Chloroacetyl chloride (5.1 ml, 67 mmoles) was added dropwise while maintaining the reaction mixture slightly basic by addition of 5% sodium bicarbonate. The reaction was stirred for 30 min after all of the acid chloride had been added. The ether layer was separated, washed with water, dried over sodium sulfate, and concentrated to dryness. The residue was crystallized from a mixture of ethyl acetate and hexane to give 10 g of crude **11**, mp 135–150° dec. An additional 6.3 g (mp 162–166°) was obtained from the mother liquors following heating with benzene. Recrystallization from acetonitrile gave a pure sample: mp 169–170° dec; infrared absorption (KBr disk) at 3375, 3330, 1660 (amide CO), 1520 (amide II) cm^{-1}. Similar conditions, generally using sodium hydroxide as base, were used for the synthesis of compounds listed in Table III.

7-Chloro-1,3-dihydro-3-hydroxy-5-(4-hydroxyphenyl)-2H-1,4-benzodiazepin-2-one (5l).—To a solution of 7.2 g (21.3 mmoles) of **11** in 75 ml of dioxane, 31.8 ml of 2 *N* sodium hydroxide was added. A solid began to form within 15 min. After stirring overnight, the solid that formed was separated by filtration (8.1 g). This material was dissolved in water and acidified by addition of 3 *N* hydrochloric acid. A crystalline solid separated (3.6 g, mp 149–150° dec, 67%). Recrystallization from aqueous dioxane gave **5l**: mp 178–179°; infrared absorption (KBr disk) 3330, 3185, 3115, 1695 (amide CO) cm^{-1}; nmr peaks (DMSO-d_6) at δ 4.73 (1 H doublet, J = 8.5 cps, C*H*OH), 6.08 (1 H doublet, J = 8.5 cps, CHO*H*).

Anal. Calcd for $C_{15}H_{11}ClN_2O_3$: C, 59.51; H, 3.66; N, 9.25. Found: C, 59.68; H, 3.88; N, 8.97.

In a similar manner, 1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one (**5b**) was prepared in 44% yield from **1b**. It crystallized from ethanol as colorless plates: mp 194–195° dec; infrared absorption (KBr disk) at 3345, 3215, 3145, 1700 (amide CO).

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.43; H, 4.90; N, 10.96.

(13) All melting points are corrected. Infrared spectra were determined using a Beckman IR-5 or IR-9 spectrophotometer, mass spectra with a CEC 21-110 spectrometer, and nmr spectra with a Varian A-60 spectrometer. Identity of compounds was established by comparison of spectra and mixture melting point. In reporting infrared and nmr data, only the significant peaks are noted.

(14) G. N. Walker, *J. Org. Chem.*, **27**, 1929 (1962).

7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one (5a).[8] (a) **5a from 1a.**—A solution of 20 g (62 mmoles) of **1a** in a mixture of 400 ml of ethanol and 125 ml of 2 *N* sodium hydroxide was stirred for 2 hr at room temperature. The solid that separated was removed by filtration to yield 7.6 g of crude sodium salt of **5a**, mp 200–220° dec. The solid was dissolved in 300 ml of 66% aqueous ethanol (pH 11.8) and acidified to pH 1.8 with 3 *N* hydrochloric acid. Filtration separated 5.4 g of **5a**, mp 197–198° dec. A second crop of 1.1 g (mp 168–184° dec) was obtained from the mother liquors. The filtrate from the sodium salt was acidified to pH 1.5 and an additional 4.85 g of crude **5a**, mp 180–182° dec, separated. Recrystallization of the crude material from ethanol yielded 3.75 g of **5a** (mp 196–198° dec) which was identical with an authentic sample.

(b) **5a from 3a.**—A solution of 1 g of **3a** in 50 ml of methanol containing 2.5 ml of 2.79 *N* sodium methoxide in methanol was stirred for 3 hr at room temperature. The solid that formed was separated by filtration (0.45 g, mp 196–210° dec) and dissolved in 50% aqueous ethanol. On acidification to pH 2 with 3 *N* hydrochloric acid, 0.3 g of **5a** (mp 198–200°) crystallized. An additional 150 mg of **5a** was isolated from the methanol mother liquors after acidification.

2,12-Dichloro-5,7-15,17-tetrahydro-10,20-diphenyl-6H,16H-dibenzo[*dl*][1,9.2,6,10,14]dioxotetraazacyclohexadecine-6,16-dione (8) and 7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one (5a) from 1a.—To a solution of 20 g (62 mmoles) of **1a** in 190 ml of dioxane, 62ml of 1 *N* sodium hydroxide was added dropwise while stirring. After 20 hr at room temperature, the solid that formed was separated by filtration to give 7.1 g of **8**, mp 317–318° dec. Recrystallization from dioxane gave a pure product: mp 318–319° dec; infrared absorption (KBr) at 3425, 1700 (amide CO), 1515 (amide II) cm^{-1}.

Anal. Calcd for $C_{30}H_{22}Cl_2N_4O_4$: C, 62.84; H, 3.87; N, 9.77; Cl, 12.37. Found: C, 62.82; H, 3.72; N, 10.13; Cl, 12.25.

The dioxane filtrate obtained above was concentrated to a small volume under reduced pressure and the residue was partitioned between chloroform and water. The organic phase was dried over sodium sulfate and concentrated to a small volume. Crystallization from a mixture of methylene chloride and hexane yielded 2.4 g of crude **5a**, mp 160–165° dec. Repeated crystallization from ethanol gave **5a** which was identical in all respects with an authentic sample.

8-Chloro-1,3-dihydro-6-phenyl-2H-4,1,5-benzoxadiazocin-2-one (3a) from 1a. Method A.—To a solution of 5 g (15 mmoles) of **1a** in 200 ml of dioxane, 15 ml of 2 *N* sodium hydroxide was added and the mixture stirred for 3 hr at room temperature. On addition of 200 ml of water to the clear yellow solution, a white precipitate formed which was removed by filtration (0.6 g, mp 296–299° dec). The filtrate was acidified to pH 6 by addition of 3 *N* hydrochloric acid and dioxane was removed by distillation under reduced pressure. The yellow oil that separated was extracted with methylene chloride and after drying over sodium sulfate, the organic solvent was distilled. Crystallization of the residue from benzene gave 0.65 g of material, mp 165–166°. On addition of hexane to the filtrate, a small amount of amorphous material separated which was removed by decanting the clear liquid. Further addition of hexane resulted in crystallization of 0.7 g of material, mp 122–135°. Thin layer chromatography of this product showed it to be a mixture of **1a** and **3a**. Concentration of the filtrate to dryness and crystallization of the residue from benzene gave 0.3 g of **3a**, mp 197–199°, identical with an authentic sample.

8-Chloro-1,3-dihydro-3-methyl-6-phenyl-2H-4,1,5-benzoxadiazocin-2-one (3g). Method A.—To a solution of 5 g (13.1 mmoles) of **1g** in 40 ml of dioxane, 13.1 ml of 2 *N* sodium hydroxide was added. After standing for 20 hr at room temperature, a small amount of insoluble material was removed by filtration. Dilution of the filtrate with water and acidification to pH 1.7 with 3 *N* hydrochloric acid produced a crystalline solid that was separated by filtration to give 3.4 g of crude **3g**, mp 145–152°. Recrystallization from a mixture of methylene chloride and hexane gave a pure product, mp 170–172°. The compound appeared to form a solvate and the higher melting point was observed only after heating for several hours at 100° under reduced pressure. It showed infrared absorption ($CHCl_3$) at 3370 (NH), 3005, 1672 (C=O) cm^{-1} and nmr peaks ($CDCl_3$) at δ 1.45 (3 H doublet, J = 7 cps, CH_3), and 4.97 (1 H quartet, J = 7 cps, CH).

8-Bromo-1,3-dihydro-6-(2-pyridyl)-2H-4,1,5-benzoxadiazocin-2-one (3f) and 7-Bromo-1,3-dihydro-3-hydroxy-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one (5f). Method A.—To a solution of 21

g (56 mmoles) of **1f** in 700 ml of dioxane, 39.9 ml of 2.79 *N* sodium methoxide was added and the solution was stirred for 20 hr at room temperature. After filtration to remove a small amount of gelatinous material, the filtrate was diluted with water and acidified to pH 4.1 by addition of 3 *N* hydrochloric acid. A light yellow solid crystallized and was separated by filtration (1.6 g, mp 322–323° dec). Dioxane was removed by distillation of the filtrate under reduced pressure and the residue was partitioned between chloroform and water. The organic layer was dried over sodium sulfate, concentrated to a small volume, then dissolved in ethyl acetate, and passed through a column of "Florisil" (14 in. × 0.75 in.). On concentration of the ethyl acetate eluates, 5.9 g of crude **3f** crystallized, mp 225–228°. Recrystallization from a mixture of tetrahydrofuran and hexane gave colorless rods: mp 229–231°; infrared absorption (KBr disk) at 3150, 1670 (C=O) cm^{-1}; nmr (DMSO-d_6) peaks at δ 4.83 (2 H quartet, J = 16.5 cps, CH_2).

Continued elution with ethyl acetate (followed by tlc) separated a second fraction which crystallized on concentration yielding 1.8 g of material melting at 212–213°. On recrystallization from acetonitrile, 250 mg of insoluble material (mp 241–243° dec) was obtained. Further crystallization of this fraction from a mixture of tetrahydrofuran and hexane raised the melting point to 253–254°. This material was identical with an authentic sample of 7-bromo-1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one 4-oxide (**19**).[15]

The acetonitrile solution crystallized yielding 1.4 g of **5f**, mp 198–200° dec. Elemental analysis and nmr indicated that the material crystallized from acetonitrile with 0.5 mole of solvent of crystallization which was difficult to remove by heating. Recrystallization from a mixture of tetrahydrofuran and hexane followed by drying at 100° gave analytically pure material showing infrared absorption (KBr disk) at 3226, 3125, 2850, 1705 (C=O) cm^{-1} and nmr peaks (DMSO-d_6) at δ 4.90 (1 H doublet, J = 8 cps, CH), 6.45 (1 H doublet, J = 8 cps, OH). With D_2O the doublet at 4.90 ppm became a singlet.

Anal. Calcd for $C_{14}H_{10}BrN_3O_2$: C, 50.62; H, 3.03; N, 12.65. Found: C, 50.92; H, 3.36; H, 12.34.

Conversion of 3f to 5f.—To a solution of 3.0 g (9 mmoles) of **3f** in 300 ml of dioxane, 9 ml of 2 *N* sodium hydroxide was added and the reaction mixture was then stirred for 20 hr. An equal volume of water was added and the pH was brought to 3.95 by addition of 3 *N* hydrochloric acid. Dioxane was then removed by distillation at reduced pressure. A yellow solid that formed was separated by filtration (0.7 g, mp 118–146°). It was very impure and only traces of **5f** could be isolated. The aqueous filtrate was extracted with methylene chloride and the organic layer was concentrated to dryness after drying over sodium sulfate. On addition of benzene to the oily residue, 1.6 g of crystalline material (mp 183–184°) was obtained. Recrystallization from acetonitrile gave 1.05 g of **5f**, mp 197–198°, which was identical with an authentic sample. Concentration of the mother liquors produced 200 mg of material, mp 255–257° dec. On recrystallization from a mixture of THF and hexane, 50 mg of **6f**, mp 273–274° dec, was isolated. This material was identical with an authentic sample. This general procedure was used to rearrange compounds of types **3** into **5**.

3-Acetoxy-7-bromo-1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one (18) and 1-Acetyl-3-acetoxy-7-bromo-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one (20).—A mixture of 8.8 g (26.5 mmoles) of **19** in 450 ml of acetic anhydride was heated rapidly to reflux and then allowed to cool slowly. After concentrating under reduced pressure to about one-half of the original volume, **18** crystallized. Filtration separated 4.2 g of **18**, mp 233–234.5° dec. Recrystallization from a mixture of tetrahydrofuran and hexane gave a pure product: mp 237–238° dec; infrared absorption (KBr disk) at 1750 (ester CO), 1695 (amide CO) cm^{-1}; nmr (DMSO) peaks at δ 2.24 (3 H singlet, CH_3) and 5.88 (1 H singlet, CH).

Anal. Calcd for $C_{16}H_{12}BrN_3O_3$: C, 51.35; H, 3.23; N, 11.23. Found: C, 51.97; H, 3.41; N, 10.93.

The acetic anhydride filtrate obtained above was concentrated to dryness under reduced pressure. Crystallization of the residue from a mixture of methylene chloride and hexane gave 1.0 g of crude **18** melting at 227–229° dec. The filtrate was again concentrated to dryness and the residue crystallized from a mixture of benzene and hexane. Filtration separated 2.0 g of **20**: mp 190–191° dec (further crystallization did not alter the melting point); infrared absorption ($CHCl_3$) 1740 (ester CO)[16] cm^{-1}; nmr ($CDCl_3$) peaks at δ 2.30 (3 H singlet, CH_3), 2.60 (3 H singlet, CH_3), 6.13 (1 H singlet, CH).

Anal. Calcd for $C_{18}H_{14}BrN_3O_4$: C, 51.93; H, 3.39; N, 10.09. Found: C, 51.88; H, 3.57; N, 10.24.

7-Bromo-1,3-dihydro-3-hydroxy-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one (5f) and 7-Bromo-5-(2-pyridyl)-4,5-dihydro-1H-1,4-benzodiazepine-2,3-dione (6f).—A solution of 1.25 g of **18** in 30 ml of ethanol and 1.6 ml of 2 *N* sodium hydroxide was heated at 50° for 3 hr. After dilution with water, the reaction mixture was neutralized with acetic acid and the crystalline product separated by filtration (1.0 g, mp 197–230° dec). On recrystallization from a mixture of tetrahydrofuran and hexane, two types of crystals were obtained. These were separated manually. One crude mixture (300 mg) melted at 204–206° dec. Three crystallizations from acetonitrile gave a homogeneous product, **5f**, mp 200–201° dec. This sample was identical in all respects with the samples of **5f** prepared above from **1f** and **3f**. The other crystalline form, 300 mg melting at 269–272°, was recrystallized from aqueous dimethylformamide without significant change in melting point. It was identical with the sample of **6f** obtained from **3f**. Infrared absorption (KBr disk) showed a broad carbonyl band with an inflection at 1680 and a peak at 1660 cm^{-1}; nmr showed (DMSO-d_6) δ 5.71 [1 H doublet, J = 7 cps, CH (position 5), doublet collapses to singlet on addition of D_2O] and 9.30 [1 H doublet, J = 8 cps, NH (position 4)].

Anal. Calcd for $C_{14}H_{10}BrN_3O_2$: C, 50.62; H, 3.03; Br, 24.06. Found: C, 50.53; H, 3.07; Br, 23.76.

2′-Benzoyl-4′-chloro-2-phthalimidoxyacetanilide (10a). Method B_1.—A solution of 10 g (28 mmoles) of 2′-benzoyl-2-bromo-4′-chloroacetanilide,[17] 4.6 g (28 mmoles) of N-hydroxyphthalimide, and 8.6 ml of triethylamine in 60 ml of tetrahydrofuran was stirred and heated to reflux for 75 min. After cooling, filtration separated triethylamine hydrobromide. On addition of hexane to the filtrate, crystallization occurred and the product was separated by filtration yielding 10 g of **10a**, mp 179–181°. Recrystallization gave a pure product: mp 183–185°; infrared absorption ($CHCl_3$) at 3330, 3040, 1795, 1740 (phthalimide CO), 1695 (amide CO), 1645 (ketone), 1510 (amide II) cm^{-1}.

2-Aminoxy-2′-benzoyl-4′-chloroacetanilide (11a).—A solution of 78 g (0.18 moles) of **10a** in a mixture of 900 ml of chloroform and 900 ml of ethanol containing 21 g of hydrazine hydrate and 21 ml of water was kept for 16 hr at room temperature. The gelatinous precipitate of phthalhydrazide that formed was separated by filtration. The filtrate was concentrated under reduced pressure, after addition of water, to remove chloroform and ethanol. The solid that separated was removed by filtration to yield 53.1 g of crude **11a**, mp 79–86°. Recrystallization from a mixture of benzene and hexane gave colorless prisms: mp 85–87°; infrared absorption ($CHCl_3$) at 3310, 3010, 1695 (amide CO), 1640 (ketone), 1515 (amide II) cm^{-1}.

2′-Benzoyl-2-carbobenzoxyaminoxy-4′-chloroacetanilide (14). Method B_2.—A solution of 12.0 g (52 mmoles) of 2-amino-5-chlorobenzophenone and 11.7 g (52 mmoles) of carbobenzoxyaminoxyacetic acid[18] in 500 ml of methylene chloride was cooled to 0° in an ice bath and a solution of 11.6 g (0.57 mmoles) of dicyclohexylcarbodiimide in 125 ml of methylene chloride was added dropwise during 1 hr. After 15 hr at room temperature, dicyclohexylurea (9.8 g, mp 232–233°) was separated by filtration. Acetic acid (3 ml) was added to the filtrate, solvent was distilled off, and the residue stirred with benzene. An additional 1.6 g of dicyclohexylurea separated. Solvent was again distilled off under reduced pressure and the residue, dissolved in methyl-

(15) Compound **19** was prepared by the reaction of 6-bromo-2-chloromethyl-4-(2-pyridyl)quinazoline 3-oxide [R. Ian Fryer, R. A. Schmidt, and L. H. Sternbach, *J. Pharm. Sci.*, **53**, 264 (1964)] with alkali. It crystallized from ethanol: mp 253° dec, nmr (DMSO-d_6) peak at δ 4.67 (2 H singlet, CH_2). *Anal.* Calcd for $C_{14}H_{10}BrN_3O_2$: C, 50.62; H, 3.03; N, 12.65. Found: C, 50.91; H, 2.98; N, 12.43.

(16) Although an amide carbonyl band at about 1700 cm^{-1} could not be observed, the structure assigned is based on the products of hydrolysis of an analogous diacetyl compound: S. C. Bell and P. H. L. Wei, *J. Org. Chem.*, **30**, 3576 (1965). Similar products, including 2-acetamido-5-chlorobenzophenone, have been isolated in our laboratory.

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

(18) M. Frankel, G. Zvilichovsky, and G. Knotler, *J. Chem. Soc.*, 3931 (1964).

ene chloride, was passed through a column of Florisil. Further elution with methylene chloride removed 3.5 g of 2-amino-5-chlorobenzophenone. Elution with ethyl acetate separated 11.7 g of material which showed two spots on tlc. Crystallization from a mixture of benzene and hexane gave 8.3 g of **14**, mp 113–114°. Further crystallization from a mixture of benzene and hexane gave a product melting at 115–116°: infrared absorption ($CHCl_3$) at 3335, 3020, 1755 (CO), 1695 (amide CO), 1645 (ketone), 1515 (amide II) cm^{-1}.

2-Aminoxy-2′-benzoyl-4′-chloroacetanilide (11a from 14).—A solution of 7.25 g of **14** in 75 ml of 20% hydrobromic acid in acetic acid was stirred for 30 min at room temperature. On addition of 750 ml of anhydrous ether, a gummy solid formed. After decantation of the supernatant, the gummy residue was partitioned between ether and 5% sodium bicarbonate. The ether layer was dried over sodium sulfate and concentrated to dryness. Crystallization of the residue from a mixture of benzene and hexane gave 2.9 g of **11a**, mp 85–86°.

8-Chloro-1,3-dihydro-6-phenyl-2H-4,1,5-benzoxadiazocin-2-one (3a) from 14.—To a refluxing stirred solution of 12.5 g of pyridine hydrochloride in 1250 ml of pyridine, a solution of 12.5 g of **11a** in 500 ml of pyridine was added slowly during 90 min. Refluxing was continued for 5 hr, then pyridine was removed by distillation under reduced pressure and the residue paritioned between methylene chloride and water. The organic layer was separated and washed with dilute hydrochloric acid, dilute sodium bicarbonate, and dried over sodium sulfate. Solvent was distilled under reduced pressure and the residue crystallized from ethyl acetate. Filtration separated 800 mg of material of unknown structure melting at 256–257°. The filtrate was concentrated to dryness and the residue crystallized from benzene to give 4.0 g of **3a**, mp 193–197°. Further crystallization from benzene gave heavy, colorless prisms: mp 198–199°; infrared absorption ($CHCl_3$) at 3335, 1675 (CO) cm^{-1}; nmr peaks ($CDCl_3$) at δ 4.85 (2 H quartet, J = 16.5 cps, CH_2).

N-(2-Amino-5-chlorodiphenylmethylene)aminoxycaetic Acid (*syn* Isomer) (16).—To a suspension of 100 g (0.4 mole) of 2-amino-5-chlorobenzophenone *syn*-oxime[7] in 1500 ml of ethanol, 43.2 g (0.8 mole) of sodium methoxide was added followed by 56 g (0.4 mole) of bromoacetic acid. The mixture was stirred and heated to reflux for 2 hr. Solvent was then removed by distillation under reduced pressure. The residue was partitioned between methylene chloride and water, the organic layer was separated, and the aqueous layer made more basic by addition of 10% sodium hydroxide. The aqueous layer was again extracted with methylene chloride and filtered through Celite to remove a small amount of insoluble material. On standing, the sodium salt of **16** crystallized. It was separated by filtration, dissolved in 2 l. of water and, on acidification with 3 N hydrochloric acid, the free acid crystallized. After recrystallization from aqueous ethanol, 52.9 g (43%) of N-(2-amino-5-chlorodiphenylmethylene)aminoxyacetic acid (*syn* isomer), mp 164–166°, was obtained: infrared absorption (KBr disk) 3440, 3370, broad COOH band, 1725 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}ClN_2O_3$: C, 59.12; H, 4.30; N, 9.19. Found: C, 58.92; H, 4.56; N, 9.30.

3a from 16. Method C.—A solution of 25.0 g (82 mmoles) of **16** in 1 l. of tetrahydrofuran was cooled to 5° and a solution of 15 g (73 mmoles) of N,N′-dicyclohexylcarbodiimide in 100 ml of tetrahydrofuran was added slowly. The mixture was stirred for 15 hr at room temperature. Filtration separated 13.4 g of dicyclohexylurea, mp 220–231°. To the filtrate, 2 ml of acetic acid was added followed by about 200 ml of water. Distillation under reduced pressure removed tetrahydrofuran. The residue was dissolved in methylene chloride and washed successively with water, 5% sodium bicarbonate, and saturated salt solution. After drying over sodium sulfate, the solvent was removed by distillation. The residue was dissolved in hot benzene and filtered to remove a small amount of insoluble material. On standing, 0.6 g of **3a** crystallized. From the mother liquor, after addition of hexane, 6.9 g of an impure **3a** crystallized, mp 184–192°. Recrystallization from benzene gave 3.0 g of product melting at 199–203°. The material was identical with an authentic sample.

N-(2-Amino-5-chlorodiphenylmethylene)aminoxyacetic Acid Ethyl Ester (*syn* Isomer) (17).—To a solution of 24.7 g (0.1 mole) of 2-amino-5-chlorobenzophenone *syn*-oxime[7] in 500 ml of ethanol and 36 ml of 2.79 N sodium methoxide in methanol, 16.7 g (0.1 mole) of ethyl bromoacetate was added. The mixture was stirred and heated to reflux for 2 hr, then concentrated to a small volume under reduced pressure. A methylene chloride solution of the residue was washed with water, dried over sodium sulfate, and concentrated to dryness under reduced pressure. The residue was dissolved in benzene and passed through a column of alumina. The benzene elutate was concentrated to dryness and crystallized from cyclohexane to give 13 g of crude **17**, mp 67–72°. Recrystallization from hexane gave colorless needles: mp 82–84°; infrared absorption ($CHCl_3$) 3450, 3350 (NH_2), 1750 (ester CO) cm^{-1}.

Anal. Calcd for $C_{17}H_{17}ClN_2O_3$: C, 61.36; H, 5.15; N, 8.42. Found: C, 61.60; H, 5.17; N, 8.69.

3a and 8 from 17.—A solution of 5 g (15 mmoles) of **17** and 2.9 g (15 mmoles) of *p*-toluenesulfonic acid monohydrate in 250 ml of xylene was stirred and heated to reflux for 20 hr. Xylene was then removed by distillation under reduced pressure and the residue was partitioned between methylene chloride and water. After drying over sodium sulfate, the organic layer was concentrated to dryness. The residue was triturated with benzene and filtered to remove 1.0 g of polymeric material, mp 291–295°. The filtrate was concentrated to dryness and triturated with ethyl acetate. Filtration separated 0.2 g of **8**, mp 311–312 dec, which melted at 318–319° dec after one crystallization and was identical with an authentic sample. The filtrate was concentrated to dryness, dissolved in methylene chloride, and adsorbed on Florisil. On elution with ether and crystallization from benzene, 0.1 g of **3a**, mp 198–200°, was obtained.

8-Chloro-1,3-dihydro-1-methyl-6-phenyl-2H-4,1,5-benzoxadiazocin-2-one (3c). Method D.—To a solution of 2.0 g (7 mmoles) of **3a** in 25 ml of dimethylformamide, 0.5 g of sodium hydride (60% in mineral oil) was added. After stirring for 15 min 2.3 g of methyliodide was added and stirring was continued for 45 min. Ice was added slowly followed by water. The solid that separated was removed by filtration; 0.7 g, mp 78–82°. Recrystallization from hexane gave 250 mg of **3c**: mp 130–132° (further crystallization did not alter the melting point); infrared absorption ($CHCl_3$) 3030, 1655 (C=O); nmr (THF-d_8) peaks at δ 3.18 (3 H singlet, CH_3), 4.71 (2 H quartet, J = 16 cps, CH_2).

2-Acetyl-6-chloro-4-phenylquinazoline (21) from 3.—A solution of 5 g (17 mmoles) of **3g** in 250 ml of methanol containing 12.2 ml of 2.79 N sodium methoxide in methanol was stirred for 20 hr at room temperature. The reaction mixture was diluted with water and acidified to pH 2 by addition of 3 N hydrochloric acid. Methanol was removed by concentration under reduced pressure. The residue was extracted with methylene chloride, dried over sodium sulfate, and concentrated to dryness. Crystallization from ether gave 800 mg of **21**, mp 122–128°. An additional 1.7 g was isolated from the mother liquors. Recrystallization from hexane gave pure material: mp 131–132°; infrared absorption ($CHCl_3$) at 1710 (ketone) cm^{-1}; nmr peak at δ 2.93 (3 H singlet, CH_3).

Anal. Calcd for $C_{16}H_{11}ClN_2O$: C, 67.97; H, 3.92; N, 9.91. Found: C, 67.82; H, 3.92; N, 9.94.

6-Chloro-4-phenyl-quinazoline-2-carboxylic acid (22)[12].—A suspension of 2.8 g of **21** in 100 ml of 10% sodium hydroxide and 20 ml of sodium hypochlorite (16.6% active chlorine) was stirred and heated on a steam bath for 4 hr. The crystal form appeared to change. After cooling, the solid was separated by filtration and partitioned between chloroform and dilute hydrochloric acid. The chloroform layer was washed with water, dried over sodium sulfate, and the solvent distilled. The residue was taken up in acetone, decolorized with Norit A, taken to dryness *in vacuo*, and crystallized from a mixture of methylene chloride and hexane to give 1.0 g of **22**, mp 213–214°, which was identical with an authentic sample.

Registry No.—**1a,** 13132-56-4; **1b,** 13132-57-5; **1c,** 13132-58-6; **1d,** 13221-15-3; **1e,** 13132-59-7; **1f,** 13132-60-0; **1g,** 13132-61-1; **1h,** 13169-25-0; **1i,** 13132-62-2; **1j,** 13132-63-3; **1k,** 13187-40-1; **1l,** 13132-64-4; **1m,** 13132-65-5; **3a,** 13132-66-6; **3b,** 13132-67-7; **3c,** 13169-26-1; **3d,** 13132-68-8; **3e,** 13132-69-9; **3f,** 13132-70-2; **3g,** 13132-71-3; **3h,** 13132-72-4; **5b,** 13127-21-4; **5f,** 13132-73-5; **5l,** 13127-22-5; **6f,** 13132-74-6; **8,** 13169-27-2; **10a,** 13132-75-7; **10b,** 13132-76-8; **10c,** 13132-77-9; **10d,** 13127-23-6; **10e,** 13132-78-0; **10f,** 13270-32-1; **10g,** 13169-28-3; **10n,** 13132-79-1; **11a,** 13132-80-4; **11d,** 13132-81-5; **11e,** 13132-82-6; **11g,** 13132-83-7; **11n,**

13132-84-8; **14**, 13132-85-9; **16**, 13132-86-0; **17**, 13132-87-1; **18**, 13132-88-2; **19**, 1694-67-3; **20**, 13132-90-6; **21**, 13132-91-7; **22**, 5958-08-7; 2-amino-5-chloro-4′-hydroxybenzophenone *syn*-oxime, 13132-93-9.

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3,7-Disubstituted Octahydro-1,5-diazocines. Their Conversion into Tetrahydro-1,5-diazocines and into Ring-Contracted Products

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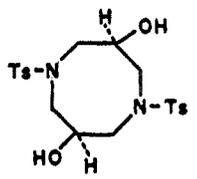
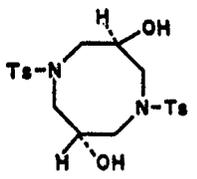
The *cis* and *trans* isomers of 1,5-bis(*p*-toluenesulfonyl)-3,7-dihydroxyoctahydro- (**1** and **2**) and of 1,5-bis-(*p*-toluenesulfonyl)-3,7-dihydroxy-3,7-dimethyloctahydro-1,5-diazocines (**5** and **6**) have been identified by spectral and chemical means. The *trans* isomer **6** readily affords the anhydro compound **7** upon treatment with acetic anhydride, while the *cis* isomer **5** is converted into the diacetyl derivative **8**. The dichloro compound **9** affords the dienes **11** and **12** when treated with sodium ethoxide. The diene **12** is the sole product when **9** is treated with potassium carbonate in dimethylformamide. The tetratosyl compounds **15** and **16** afford, in addition to the dienes **11** and **12**, the monoene-monool **14**. Treatment of the diols **1** and **2** with thionyl chloride affords the piperazine **17** and the diazepine **18**. The structures of the various compounds are established by chemical and spectral means.

We have recently described[1] the synthesis of the *cis*- and *trans*-1,5-bis(*p*-toluenesulfonyl)-3,7-dihydroxyoctahydro-1,5-diazocines. While the nuclear magnetic resonance (nmr) spectra of the two compounds strongly imply their stereochemistry (the low melting isomer corresponding to the *cis* isomer **1** and the high melting isomer corresponding to the *trans* isomer **2**), it is still necessary to confirm these tentative assignments by additional studies.



1



2

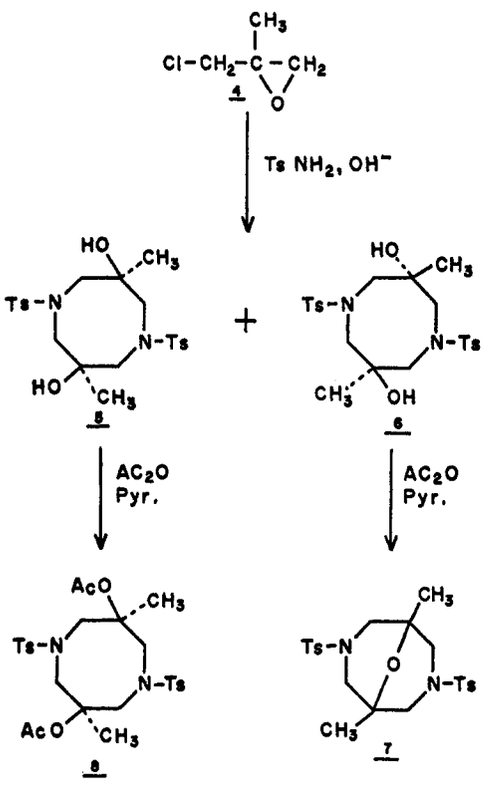
The treatment of the epoxide **4** with *p*-toluenesulfonamide in base, under conditions similar to those described for the preparation of the diols **1** and **2**, afforded the two isomeric diols **5** and **6** (Scheme I).

The methylene protons (H_A and H_B, J_{AB} = 15 cps) of the high melting diol **5** resonate at τ 5.93 and 7.09, while the corresponding protons (H_A and H_B, J_{AB} = 16 cps) of the low melting diol **6** resonate at τ 6.20 and 6.60, respectively. An examination of Dreiding models of the two isomers clearly shows that the methylene protons in the *trans* isomer are more nearly magnetically equivalent than those in the *cis* isomer. Consequently, the high melting diol should be the *cis* isomer **5**, and the low melting diol should be the *trans* isomer **6**.

The structural assignment is further confirmed by the results of acetylation studies on the two isomers. The *trans* isomer **6** forms the anhydro derivative **7** exclusively, while the *cis* isomer **5** forms the 3,7-diacetyl compound **8** only.

This analysis can now be used to further confirm the stereochemical assignment of the diols **1** and **2**. The chemical shift difference between the methylene protons

SCHEME I



of the low melting diol **1** is 0.89 ppm while it is essentially nil[1] in the high melting diol **2**. This is in agreement with the assignment deduced from both nmr and chemical evidence for the tertiary diols **5** and **6**, and consequently proves the structures of the diols **1** and **2**. The differences in the melting points of the two series (the *cis* compound **1** is the low melting isomer, while the *cis* compound **5** is the high melting one in the dimethyl series) is of some interest. These melting point differences are no longer present in any of the derivatives of the two different diol series. The relative positions on thin layer chromatographic plates are the same for the two series of diols (the *trans* isomer being the one with a higher R_f value in both cases).

(1) W. A. Paudler, G. R. Gapski, and J. M. Barton, *J. Org. Chem.*, **31**, 277 (1966).