4-Substituted-3,4-dihydro-3-methyl-2*H*-1,3-benzoxazin-2-ones. III (2,3). Solvolytic-Reductive Transformation of 4-(2-Keto)-benzoxazin-2-ones into Oxazin-2-ones

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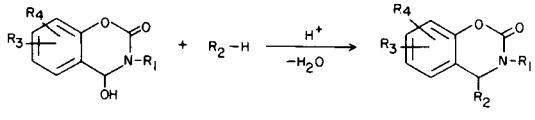
A series of 4-(2-keto-substituted)-3,4-dihydro-3-methyl-2*H*-1,3-benzoxazin-2-ones **1** (Table I) was synthesized by condensation of 3-alkyl-3,4-dihydro-4-hydroxy-2*H*-1,3-benzoxazin-2-ones **4** with ketones **5** having active *alpha* hydrogens. In the presence of alcoholic potassium borohydride, compounds **1** underwent reductive transacylation to give 1,3-oxazin-2-one derivatives **3** (Table III, a,b,c). When the other side of the ketone possessed substituents other than hydrogen, there were always also normal reduction products, *i.e.*, secondary alcohols **2** (Table II) in addition to **3**.

J. Heterocyclic Chem., **17**, 277 (1980).

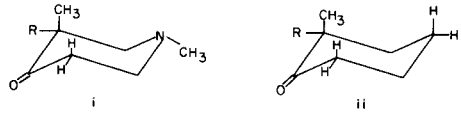
In the previous papers of this series (2,3) we had described a facile, acid-catalyzed condensation of 3-alkyl-3,4-dihydro-4-hydroxy-2*H*-1,3-benzoxazin-2-ones **4** with compounds having active hydrogens, **5** to give 4-substituted derivatives of general type **1a,b**.



4 5 1a, R_2 = carbamate, aryl, heterocycle, ketone (2)
1b, R_2 = urea or thiourea (3)

This paper describes the utilization of straight-chained or cyclic ketones **5** as the nucleophile. The condensations were generally accomplished in benzene under azeotropic conditions in the presence of traces of mineral acids (Method A). In some instances, when the ketone **5** contained basic nitrogen, a solution of **4** and **5** in *N,N*-dimethylformamide was saturated with dry hydrogen chloride and allowed to stand at room temperature for a prolonged period of time (Method B). Symmetrical ketones **5** (usually in slight excess) condensed with **4** to give mono-condensation products practically quantitatively. When two equivalents of **4** were used, the bis-benzoxazine derivatives **1** resulted (Table I).

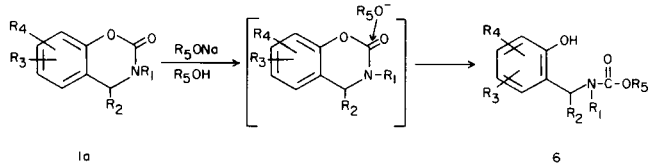
Asymmetric ketones **5** normally condensed with **4** on the least hindered side of the carbonyl group. An exception was 3-methyl-4-piperidinone which condensed exclusively on the more hindered side. This was especially striking since the similar compound, 2-methylcyclohexanone reacted normally. The discrepancy between these two cases can be rationalized on the basis of steric crowding of the products. Thus, there is only one 1,3-methyl-hydrogen interaction in the former case (i) and two in the latter case (ii).



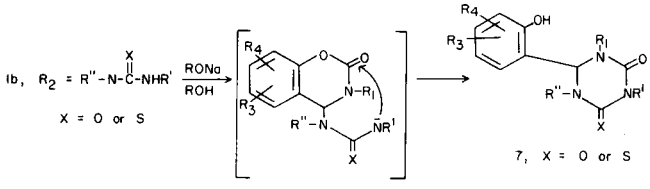
i ii

When a second equivalent of **4** was available, condensation of **1g** to bis-benzoxazine derivative **1h** took place.

Compounds of type **1a** were shown (2) to be sensitive towards alcoholic alkali and underwent cleavage of the heterocyclic ring to form open-chained phenolic carbamates **6** (2), whenever the 4-substituent (R_2) did not contain any functional group capable of participating in the reaction. In cases when R_2 was an urea (**1b**), the cleavage was followed by recyclization giving the symmetrical 1,3,5-triazine-2,4-dione derivatives of type **7** (3).

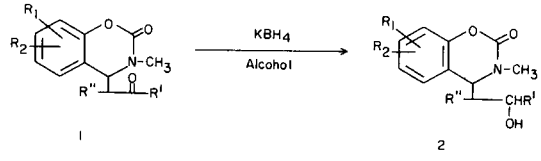


1a 6



1b, R_2 = R"-N-C(=X)-NHR' ; X = O or S 7, X = O or S

We had been interested in reducing the ketone derivatives **1** (R_2 = R"-C(=O)-C(=O)-CHR') by potassium borohydride to the corresponding alcohols **2**.



1 2

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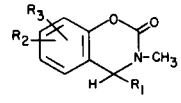
Table I

4-(2-Keto substituted)-3,4-dihydro-3-methyl-2*H*-1,3-benzoxazin-2-ones



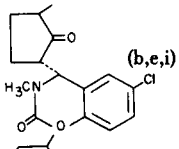
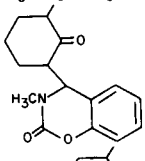
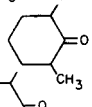
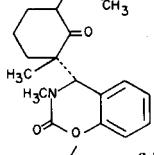
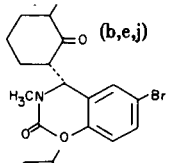
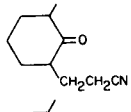
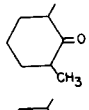
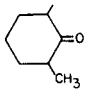
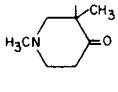
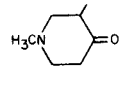
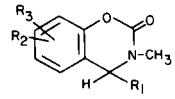
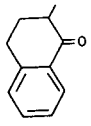
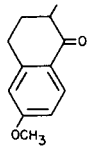
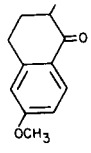
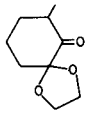
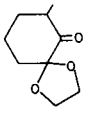
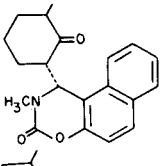
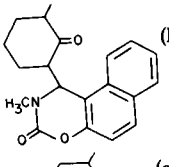
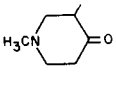
Compound	R_1	R_2	R_3	M.p. °C	% Yield	Empirical Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1c		H	H	111-112	61	$C_{14}H_{15}NO_3$	68.55	6.16	5.71	68.64	6.05	5.80
1d		6-Cl	H	153-154	57	$C_{14}H_{14}ClNO_3$	60.11	5.04	5.01	60.17	5.05	4.93
1e	 (b,e,i)	6-Cl	H	264-265 (a)	68	$C_{23}H_{20}Cl_2N_2O_5$	58.12	4.23	5.89	58.08	4.14	5.97
1f	 (d)	H	H	257-258 (a)	66	$C_{24}H_{24}N_2O_5$	68.56	5.75	6.66	68.28	5.58	6.90
1g		H	H	142-143	59	$C_{16}H_{19}NO_3$	70.31	7.01	5.13	70.09	7.01	5.22
1h		H	H	269-270 (a)	62	$C_{25}H_{26}N_2O_5$	69.11	6.03	6.45	69.28	6.08	6.61
1i	 (b)	6-Br	H	161-162	66(f)	$C_{15}H_{16}BrNO_3$	53.27	4.77	4.14	53.28	4.70	4.09
1j	 (b,e,j)	6-Br	H	273-274 (a)	23(f)	$C_{24}H_{22}Br_2N_2O_5$	49.85	3.83	4.84	49.64	3.84	4.77
1k		6-Cl	H	153-154	73	$C_{18}H_{19}ClN_2O_3$	62.52	5.25	8.10	62.23	5.46	7.93
1l		6-Br	H	173-174	54	$C_{16}H_{18}BrNO_3$	54.56	5.15	3.96	54.44	5.18	3.88
1m		8-OCH_3	H	153-154	65	$C_{17}H_{19}NO_4$	67.76	6.36	4.65	67.81	6.34	4.53
1n	 (c)	H	H	170-171	76	$C_{16}H_{20}N_2O_3$	66.64	6.99	9.72	66.93	6.99	9.62
1o	 (c)	6-Cl	H	140-141	73	$C_{15}H_{17}N_2O_3$	58.35	5.55	9.07	58.39	5.60	8.89

Table I continued

4-(2-Keto substituted)-3,4-dihydro-3-methyl-2*H*-1,3-benzoxazin-2-ones

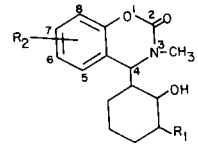


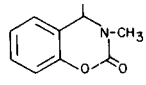
Compound	R_1	R_2	R_3	M.p. °C	% Yield	Empirical Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1p		H	H	181-182	62	$C_{19}H_{17}NO_3$	74.25	5.58	4.56	74.36	5.80	4.35
1q		H	H	160-161 (a)	79	$C_{20}H_{19}NO_4$	71.20	5.68	4.15	71.45	5.77	4.07
1r	 (b,k)	6-Cl	H	194-195	71	$C_{20}H_{18}ClNO_4$	64.61	4.88	3.77	64.73	4.86	3.78
1s		H	H	201-202 (a)	57	$C_{17}H_{19}NO_5$	64.34	6.04	4.41	64.44	5.98	4.64
1t		6-Cl	H	190-191 (a)	34	$C_{17}H_{18}ClNO_5$	58.04	5.16	4.01	57.95	5.23	4.06
1u		R_2,R_3 = 5,6		123-124	85	$C_{16}H_{15}NO_3$	71.36	5.61	5.20	71.24	5.57	5.46
1v		"		190-191	82	$C_{19}H_{19}NO_3$	73.76	6.19	4.53	73.90	6.18	4.49
1w	 (g)	"		281-282 (a)	56	$C_{32}H_{28}N_2O_5$	73.83	5.42	5.38	73.93	5.52	5.16
1x	 (h)	R_2,R_3 = 5,6 		281-282 (a)	19	$C_{32}H_{28}N_2O_5$	73.83	5.42	5.38	74.03	5.59	5.46
1y	 (c)	"		241-242 (a)	81	$C_{19}H_{20}N_2O_3 \cdot HCl$	63.24	5.87	7.76	63.25	5.91	7.71

(a) Melts with decomposition. (b) Prepared *via* Method A. (c) Prepared *via* Method B. (d) The bis-product appears to have *cis*-configuration since both *N*-methyl groups resonate at the same field. (e) Nonequivalent *N*-methyl groups. (f) Both, **1i** and **1j** (bis-product) were isolated from the same reaction giving a total of 89% yield. (g) This isomer appears to be *trans*; its *N*-methyl groups are nonequivalent. (h) *cis*-isomer; equivalent *N*-methyl groups. (g,h) Both isomers show difference in mobility. The melting points of each isomer are identical; however, a mixture melting point shows depression by about 20°. The combined yield amounts to 75% (see experimental procedure). (i) Calcd: Cl, 14.92, Found: C, 14.87. (j) Calcd: Br, 27.64, Found: Br, 27.67. (k) Calcd: Cl, 9.54, Found: Cl, 9.61.

Table II

3,4-Dihydro-4-(2-hydroxy-3-alkylcyclohexyl)-3-methyl-2*H*-1,3-benzoxazin-2-ones

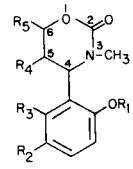


Compound	R_1	R_2	M.p. °C	% Yield	Empirical Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2a	CH_3	H	155-156	14.5 (a)	$C_{16}H_{21}NO_3$	69.79	7.69	5.09	70.09	7.72	5.04
2b	CH_3	6-Br	201-202	23	$C_{16}H_{20}BrNO_3$	54.25	5.69	3.95	54.42	5.77	3.80
2c	CH_3	8-OCH_3	191-192	24 (b)	$C_{17}H_{23}NO_4$	66.86	7.59	4.59	66.98	7.53	4.37
2d	$(CH_2)_2CN$ (f)	6-Cl	200-201	15.5 (c)	$C_{18}H_{21}ClN_2O_3$	61.98	6.07	8.03	61.95	6.13	8.33
2e		H	296-297 (e)	31 (d)	$C_{24}H_{26}N_2O_5$	68.23	6.20	6.63	68.49	6.34	6.49
2f		6-Cl	219-220	67	$C_{17}H_{20}NO_5$	57.71	5.70	3.96	57.76	5.64	3.91

(a) The combined yield of **2a** and of rearranged phenolic product **3j** amounts to 67.5%. (b) The combined yield of **2c** and **3m** is 63%. (c) Total yield of **2d** and **3l** is 69.5%. (d) Total yield of **2e** and **3n** is 79%. In this particular case the secondary alcohol **2e** was isolated first due to its lesser solubility in methanol. (e) Melts with decomposition. (f) Calcd: Cl, 10.16, Found: Cl, 10.02.

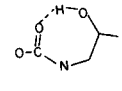
Table IIIa

Tetrahydro-4-(2-hydroxy-1-aryl)-3-methyl-2*H*-1,3-oxazin-2-ones



Compound	R_1	R_2	R_3	R_4	R_5	M.p. °C	% Yield	Empirical Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
3a	H	H	H	H	CH_3	246-247	75	$C_{13}H_{15}NO_3$	65.14	6.83	6.33	64.84	6.84	6.36
3b	$COCH_3$	H	H	H	CH_3	178-179	82	$C_{14}H_{17}NO_4$	63.86	6.51	5.32	63.69	6.57	5.29
3c	H	H	H	CH_3CHOH	CH_3	191-192 (a)	60	$C_{14}H_{19}NO_4$	63.38	7.22	5.28	63.68	6.95	5.38
3d	$COCH_3$	H	H	$CH_3CHOCOCH_3$	CH_3	158-159	60	$C_{18}H_{23}NO_6$	61.88	6.64	4.01	61.90	6.53	4.07
3e	H	R_2,R_3 = 		H	CH_3	216-217 (a)	65	$C_{16}H_{17}NO_3$	70.83	6.32	5.16	70.89	6.27	5.42

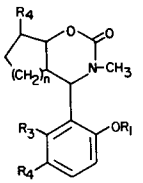
(a) Melts with decomposition.

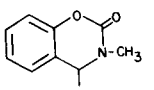
In the simplest example when R_2 was $-CH_2\overset{O}{\overset{\|}{C}}-CH_3$ **(1a)** (2), the reduction product showed correct elemental analyses, but its spectral data were in disagreement with structure **2**. The infrared spectrum of cyclic carbamate **1a** at about 1725 cm^{-1} was no longer present and the carbonyl (carbamate) absorption band was now shifted to much lower frequency at 1665 cm^{-1}. At first, a strong hydrogen-bonded cyclic carbamate  was assumed (2) to account for this dramatic shift in absorption frequency. The proton magnetic resonance spectrum (deuteriochloroform) showed phenolic proton at δ 9.67 (deuterium oxide-exchangeable) ppm. The compound gave a strong positive ferric chloride test and, on treatment with acetic anhydride at room temperature, gave acetate ester **3b** with its absorption band at 1764 cm^{-1} (characteristic of $ArOCOCH_3$), the cyclic carbamate absorption now being shifted to slightly higher frequency at 1676 cm^{-1}.

These data show clearly that the transformation occurred similar to that when urea derivatives were treated with alkali (3) giving 1,3,5-triazine-2,4-diones **7**. However, in the present case the reduction of the ketone to alcohol is accompanied by a simultaneous ring-opening and cycliza-

Table IIIb

Octahydro-4-(2-hydroxyphenyl)-3-methyl-2*H*-1,3-benzoxazin-2-ones
and octahydro-4-(2-hydroxyphenyl)-3-methylcyclopent[*e*]-1,3-oxazin-2-ones

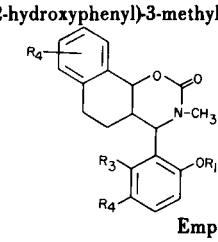


Compound	n	R_1	R_2	R_3	R_4	M.p. °C	% Yield	Empirical Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
3f	2	H	H	H	H	259-260 (a)	65	$C_{15}H_{19}NO_3$	68.94	7.33	5.36	68.66	7.26	5.57
3g	2	$COCH_3$	H	H	H	200-201 (a)	76	$C_{17}H_{21}NO_4$	67.31	6.91	4.62	67.46	6.87	4.72
3h	1	H	H	H	H	229-230 (a)	59	$C_{14}H_{17}NO_3$	67.99	6.93	5.66	68.20	6.96	5.43
3i	1	H	5-Cl	H	H	238-239 (a)	64	$C_{14}H_{16}ClNO_3$	59.68	5.72	4.97	59.60	5.69	5.14
3j	2	H	H	H	CH_3	258-259 (a)	53 (b)	$C_{16}H_{21}NO_3$	69.79	7.69	5.09	69.71	7.70	5.06
3k	2	$CONHCH_3$	H	H	CH_3	223-223 (a)	69	$C_{18}H_{24}N_2O_4$	65.04	7.28	8.43	65.24	7.35	8.43
3l	2	H	5-Cl (f)	H	$(CH_2)_2CN$	208-209 (a)	54 (c)	$C_{18}H_{21}ClN_2O_3$	61.98	6.07	8.03	61.99	6.11	8.29
3m	2	H	H	H	OCH_3	231-232 (a)	39 (d)	$C_{17}H_{23}NO_4$	66.86	7.59	4.59	66.91	7.48	4.57
3n	2	H	H	H		295-296 (a)	31 (e)	$C_{24}H_{26}N_2O_5$	68.23	6.20	6.63	68.49	6.34	6.49

(a) Melts with decomposition. (b,c,d,e) See explanation at Table II. (f) Calcd: Cl, 10.16. Found: Cl, 10.24.

Table IIIc

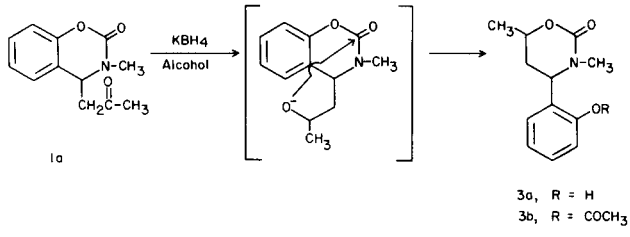
3,4,4a,5,6,10b-Hexahydro-4-(2-hydroxyphenyl)-3-methyl-2*H*-naphth[2,1-*e*]-1,3-oxazin-2-ones



Compound	R_1	R_2	R_3	R_4	M.p. °C	% Yield	Empirical Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
3o	H	H	H	H	272-273 (a)	77	$C_{19}H_{19}NO_3$	73.76	6.14	4.53	73.60	6.18	4.32
3p	H	H	H	8-OCH_3	268-269 (a)	74	$C_{20}H_{21}NO_4$	70.78	6.24	4.13	70.74	6.29	4.09
3q	H	5-Cl (b)	H	8-OCH_3	283-284 (a)	76	$C_{20}H_{20}ClNO_4$	64.26	5.39	3.75	64.53	5.64	3.91
3r	$CONHCH_3$	5-Cl (c)	H	8-OCH_3	256-257 (a)	72	$C_{22}H_{23}ClN_2O_5$	61.33	5.38	6.50	61.55	5.45	6.37

(a) Melts with decomposition. (b) Calcd: Cl, 9.48; Found: Cl, 9.58. (c) Calcd: Cl, 8.23, Found: Cl, 8.18.

tion to give a new, saturated ring system and the product is oxazine derivative **3a**.

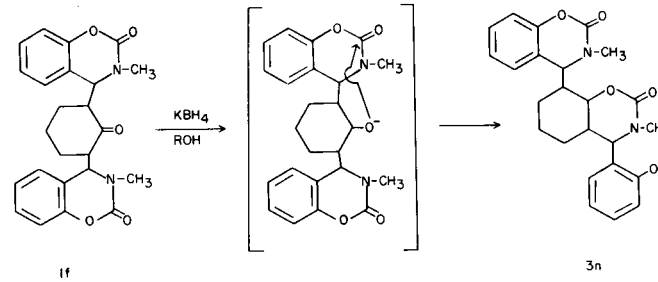


The detailed pmr analysis (see experimental) is in full agreement with structure **3a**. The *beta* diketone substituents (2) follow the same pattern and rearrange to give products having both phenolic and aliphatic hydroxyl groups in the new molecules. The new monocyclic oxazines **3** are listed in Table IIIa.

The 4-(2-keto)-substituents in the cyclic form underwent the same reductive-rearrangement giving bicyclic products (Table IIIb). The 4-substituents constituting bicyclic ketones gave tricyclic products (Table IIIc).

In the most instances the products **3**, although possessing multiple asymmetric centers and, hence, giving the possibility of numerous *d,l*-pairs, constituted single entities, having sharp melting points.

The cyclic ketone derivatives **1**, having a substituent on the other side *alpha* to the carbonyl function, in addition to the rearranged products **3**, also gave normal secondary alcohols, the benzoxazine rings remaining unchanged. Depending on the size of the substituent, the yields of secondary alcohols (Table II) were in the range of 20 to 90%. Thus, when the substituent was small alkyl (*e.g.*, CH_3, CH_2CH_2CN), yields of alcohols were 20-30%; with large substituents (*e.g.*, bis-benzoxazinone, **1f**), there was about 50/50% mixture of rearranged product and secondary alcohol. In the latter case one benzoxazine ring was cleaved and recyclized to give oxazine **3n**, while the second ring remained unaffected. The reaction must have followed the course shown below.



In the extreme case, *i.e.*, dioxolane derivative **1s**, where the *alpha* substituent was very bulky, the normal secondary alcohol was the only isolated material, and the rearranged product constituted only about 10%.

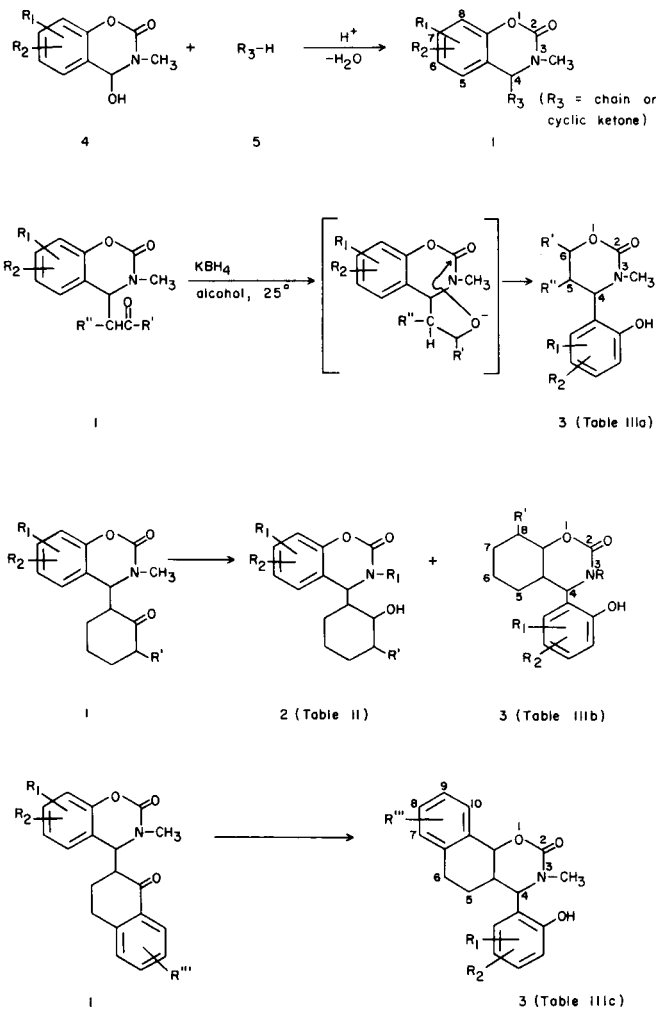
The bicyclic ketone derivatives, where the 3-substituent constituted part of the aromatic ring (*e.g.*, 3,4-dihydro-1-(2*H*)naphthalenone) gave only rearranged products **3o, p,q**.

Because of the difference in polarities and, hence, in solubilities between the rearranged products and secondary alcohols, it was relatively easy to isolate and separate them. As expected, the rearranged products, having lower solubilities, were usually isolated first, the mother liquor containing mostly the secondary alcohols. The sequence of transformations is presented in Scheme I.

In this study we had shown that the borohydride reagent performed the dual action of reducing the ketone function to alcohols and (although a much weaker base than the alkali) caused partial or total cleavage of the benzoxazine ring. This cleavage was followed by transacylation giving oxazine derivatives under mild reaction conditions. The latter compounds are stable towards such strong bases as sodium alkoxides under ordinary conditions and can be decomposed only by boiling aqueous

alkali. These findings also show that the aromatic carbamates are very unstable towards strong inorganic bases.

Scheme I



EXPERIMENTAL

Physical constants, yields, and analytical values for the compounds below are reported in Tables I, II, IIa, IIIb, IIIc. Melting points were determined using a Thomas-Hoover capillary melting point apparatus which was calibrated against known standards. The ultraviolet and infrared spectra were obtained, respectively, with a Beckman DK-1 spectrophotometer and a Baird Model 455 double-beam spectrograph. Unless otherwise stated, the former were determined as solution in 95% ethanol and the latter as Nujol mulls. The pmr spectra were recorded on a Varian A-60 spectrometer with tetramethylsilane as an internal reference. Thin layer chromatography was carried out on silica gel G (Stahl) using methanol-acetonitrile-acetone in varying proportions, as the eluent. The chromatograms were developed in an iodine chamber. The proton magnetic resonance (pmr) spectral data were included whenever they contributed to the elucidation or confirmation of structures. The aromatic proton resonances were usually not included. The emphasis was made rather on the various groups and protons critical for the particular structural assignments. Occasionally, the resonances of lone protons were not specified if they were buried under an envelope of other aliphatic protons.

The synthetic methods both for the ketone derivatives (Table I) as well as for the reaction products (Tables II, IIIa, IIIb and IIIc) were usually described in detail for the particular types as examples, other compounds in the tables having only all analytical and physical data.

3,4-Dihydro-3-methyl-4-(2-oxocyclopentyl)-2*H*-1,3-benzoxazin-2-one (**1c**, Table I).

A solution of 10.0 g. (0.056 mole) of 3,4-dihydro-4-hydroxy-3-methyl-2*H*-1,3-benzoxazin-2-one (**4a**, R_1, R_2 = H) (2), 5.2 g. (0.062 mole) of cyclopentanone and 0.01 g. of 4-methylbenzenesulfonic acid monohydrate was refluxed 2 hours, while 1.0 ml. of water separated in a Dean-Stark trap. The solution was evaporated to dryness *in vacuo* and the residue crystallized from isopropyl ether giving 8.3 g. (61% yield) of **1c** as white crystals, m.p. 111-112°; uv λ max (ethanol): nm (ε) 266 (1000), 272 (950); ir (nujol): 1714 (OCON and ketone C=O); ir (chloroform): 1730-1715 (broad band, both carbonyls) cm^{-1}.

4,4'-(2-Oxo-1,3-cyclohexanediyl)bis[3,4-dihydro-3-methyl-2*H*-1,3-benzoxazin-2-one] (**1f**).

A solution of 10.7 g. (0.06 mole) of 3,4-dihydro-4-hydroxy-3-methyl-2*H*-1,3-benzoxazin-2-one (**4a**) and 2.9 g. (0.03 mole) of cyclohexanone and 0.02 g. of 4-methylbenzenesulfonic acid monohydrate in 350 ml. of dry benzene was refluxed for 2 hours, while 1.1 ml. of water separated in a Dean-Stark trap. The solution was evaporated and the residue was crystallized from acetonitrile giving 8.3 g. (66% yield) of pure dimer **1f** as white crystals, m.p. 257-258° dec.; uv λ max (ethanol): nm (ε) 267 (2200), 273 (2100); ir (nujol): 1720 (C=O and OCON, coinciding); (chloroform): 1725-1705 (broad band of both carbonyls) cm^{-1}; pmr (deuteriochloroform): δ 3.02 [6H, s ($N\text{-}CH_3$)$_2$, equivalent], 5.03 [2H, d, J = 4.5 Hz, ($ArCH$)$_2$, equivalent] ppm.

3,4-Dihydro-3-methyl-4-(3-methyl-2-oxocyclohexyl)-2*H*-1,3-benzoxazin-2-one (**1g**).

A solution of 7.1 g. (0.04 mole) of 3,4-dihydro-4-hydroxy-3-methyl-2*H*-1,3-benzoxazin-2-one (**4a**), 4.9 g. (0.077 mole) of 2-methylcyclohexanone and 0.01 g. of 4-methylbenzenesulfonic acid monohydrate in 200 ml. of benzene was refluxed for 2 hours while the theoretical amount of water separated in a Dean-Stark trap. After the solution was evaporated to dryness *in vacuo*, the residue was crystallized from ethyl acetate-isopropyl ether giving 6.5 g. (59% yield), m.p. 141-142°. An analytical sample of **1g**, melting at 142-143°, was obtained by recrystallization from acetonitrile-ethyl acetate; uv λ max (ethanol): nm (ε) 266 (980), 272 (900); ir (nujol): 1715 (OCON), 1706 (ketone C=O) cm^{-1}; ir (chloroform): 1723 (OCON), 1711 (ketone C=O) cm^{-1}; pmr (deuteriochloroform): δ 1.16 (3H, d, J = 6.5 Hz, $C\text{-}CH_3$), 3.12 (3H, $N\text{-}CH_3$), 5.17 (1H, d, J = 4.5 Hz, $ArCH$) ppm.

4,4'(1-Methyl-2-oxo-1,3-cyclohexanediyl)bis[4,3-dihydro-3-methyl-2*H*-1,3-benzoxazin-2-one] (**1h**).

A solution of 9.2 g. (0.0516 mole) of 3,4-dihydro-4-hydroxy-3-methyl-2*H*-1,3-benzoxazin-2-one (**4a**), 2.9 g. (0.0258 mole) of 2-methylcyclohexanone, and 0.01 g. of 4-methylbenzenesulfonic acid monohydrate in 200 ml. of benzene was refluxed, while the liberated water was separated in a Dean-Stark trap. After 45 minutes of refluxing, the tlc (acetone-benzene-heptane, 2:2:1) showed practical conversion to the mono-product **1g**, R_f = 0.4 and an excess of starting **4**. The refluxing was continued for 90 minutes while 0.93 ml. of water had separated, and the tlc showed complete conversion to the bis-derivative **1h**, R_f = 0.18. After the solution was concentrated to about 40 ml. and cooled, 6.9 g. (62% yield) of **1h** as white crystals was obtained, m.p. 268-269°. An analytical sample was obtained by recrystallization from acetonitrile, m.p. 269-270 dec.; pmr (deuteriochloroform): δ 1.03 (3H, $C\text{-}CH_3$), 2.95 (3H, $N\text{-}CH_3$), 3.08 (3H, $N\text{-}CH_3$), 4.81 (1H, s, $ArCH\text{-}C\text{-}CH_3$), 5.10 (1H, d, J = 3.5 Hz, $Ar\text{-}CH\text{-}CH$) ppm.

3-(6-Chloro-3,4-dihydro-3-methyl-2-oxo-2*H*-1,3-benzoxazin-4-yl)-2-oxocyclohexanepropanenitrile (**1k**).

A solution of 10.0 g. (0.047 mole) of 6-chloro-3,4-dihydro-4-hydroxy-

3-methyl-2*H*-1,3-benzoxazin-2-one (**4b**, R_1 = H, R_2 = 6-Cl) (2), 7.8 g. (0.052 mole) of 2-oxocyclohexanepropanenitrile and 0.02 g. of 4-methylbenzenesulfonic acid monohydrate in 200 ml. of benzene was refluxed for 90 minutes while 0.85 ml. of water had separated. After the solvent was removed *in vacuo*, the residue was crystallized from isopropyl ether giving 11.8 g. (75% yield) of **1k** as white crystals, m.p. 153-154°. An analytical sample, m.p. 154-155°, was obtained by recrystallization from ethyl acetate-isopropyl ether; uv λ max (ethanol): nm (ε) 229 (7800), 276 (1270), 285 (1200); ir (chloroform): 2280 (CN), 1725 (OCON), 1716 (ketone C=O), cm^{-1}; pmr (deuteriochloroform): δ 3.06 (3H, N-CH_3), 5.06 (1H, d, J = 3.5 Hz, ArC*H*) ppm.

3,4-Dihydro-4-(1,3-dimethyl-4-oxo-3-piperidinyl)-2*H*-1,3-benzoxazin-2-one (**1n**).

A solution of 10.0 g. (0.056 mole) of 3,4-dihydro-4-hydroxy-3-methyl-2*H*-1,3-benzoxazin-2-one (**4a**) and 8.2 g. (0.056 mole) of 1,3-dimethyl-4-piperidinone in 65 ml. of dry *N,N*-dimethylformamide was treated with dry hydrogen chloride to *p*H 1.0 and the spontaneously warmed (50°) solution was allowed to stand for 5 days at room temperature. The resulting solid hydrochloride of **1n** (3.7 g., m.p. 234-235° dec.) was collected and the filtrate was evaporated to dryness *in vacuo* at 50°. Crystallization of the solid residue from acetonitrile gave 13.2 g. of the hydrochloride of **1n** (total yield, 93%), m.p. 233-234° dec. Because of the low solubility of the salt, the base was regenerated by adding of aqueous ammonia at 0° and extracting twice with 250 ml. of ethyl acetate. The combined extracts were dried with sodium sulfate and concentrated to a low volume giving 8.2 g. of analytically pure white crystals, m.p. 170-171°. Further concentration of the mother liquor gave 3.4 g. of additional product (total yield of the base, 76%), m.p. 169-170°; uv λ max (ethanol): nm (ε) 267 (1200), 274 (1150); ir (chloroform): 1725 (OCON), 1715 (ketone C=O) cm^{-1}; pmr (deuteriochloroform): δ 0.91 (3H, s, C-CH_3), 2.34 (3H, N-CH_3), 3.01 (3H, OCON CH_3), 5.44 (1H, ArC*H*) ppm.

6-Chloro-3,4-dihydro-3-methyl-4-(1-methyl-4-oxo-3-piperidinyl)-2*H*-1,3-benzoxazin-2-one (**3o**).

A solution of 21.35 g. (0.1 mole) of 6-chloro-3,4-dihydro-4-hydroxy-3-methyl-2*H*-1,3-benzoxazin-2-one (**4b**) in 25 ml. of dry *N,N*-dimethylformamide was added at 50° to a solution of 13.0 g. (0.115 mole) of 1-methyl-4-piperidine in 50 ml. of *N,N*-dimethylformamide, treated with dry hydrogen chloride to *p*H 1.0. After 3 days at room temperature, 13.4 g. of white crystals separated, m.p. 258-259° dec. The filtrate was evaporated *in vacuo* at 45°. The residue was taken up with 75 ml. of acetonitrile and refluxed for 0.5 hours to give 19.2 g. of white crystalline product, m.p. 259-260° dec. (total yield of the hydrochloride: 94%). An analytical sample of **3o**, m.p. 260-261° dec., was obtained by the recrystallization from acetonitrile. The free base was obtained by treatment of the hydrochloride with aqueous ammonia at 0°, extraction with ethyl acetate, and drying with sodium sulfate. Concentration to a low volume and cooling gave analytically pure white crystals, m.p. 140-141°; uv λ max (ethanol): nm (ε) 224 (8400), 276 (1300); ir (nujol): 1723 sh, 1712 (C=O) cm^{-1}.

3,4-Dihydro-3-methyl-4-(1,2,3,4-tetrahydro-1-oxo-2-naphthalenyl)-2*H*-1,3-benzoxazin-2-one (**1p**).

A solution of 10.0 g. (0.056 mole) of 3,4-dihydro-4-hydroxy-3-methyl-2*H*-1,3-benzoxazin-2-one (**4a**), 8.2 g. (0.056 mole) of 3,4-dihydro-1-(2*H*)-naphthalenone and 0.01 g. of 4-methylbenzenesulfonic acid monohydrate was refluxed for 90 minutes, while 1.0 ml.of water separated in a Dean-Stark trap. After the solution was evaporated to dryness, the residue was crystallized from cyclohexane-ethyl acetate giving 10.6 g. (62% yield) of analytically pure white crystals of **1p**, m.p. 181-182°; uv λ max (ethanol): nm (ε) 251 (13,850), 291 (1850); ir (nujol): 1720 (cyclic carbamate), 1672 (ArC=O) cm^{-1}.

3,4-Dihydro-3-methyl-4-(1,2,3,4-tetrahydro-6-methoxy-1-oxo-2-naphthalenyl)-2*H*-1,3-benzoxazin-2-one (**1q**).

A solution of 4.0 g. (0.0224 mole) of 3,4-dihydro-4-hydroxy-3-methyl-2*H*-1,3-benzoxazin-2-one (**4a**), 3.9 g. (0.0224 mole) of 3,4-dihydro-6-methoxy-1-(2*H*)naphthalenone and 0.01 g. of 4-methylbenzenesulfonic acid monohydrate in 120 ml. of benzene was refluxed 1 hour while 0.4 ml. of water had separated. After the solution was evaporated *in vacuo*, the solid colorless residue was crystallized from 2-propanol giving 6.0 g. (79% yield) of **1q** as white crystals, m.p. 160-161° dec.; uv λ max (ethanol): nm (ε 223 (14,300), 277 (16,800), 288 sh (16,000); ir (nujol): 1720 (OCON), 1658 (ketone C=O); pmr (deuteriochloroform): δ 3.11 (3H, NCH_3), 3.75 (3H, OCH_3), 5.50 (1H, d, J = 3.5, ArC*H*) ppm.

3,4-Dihydro-3-methyl-4-(6-oxo-1,4-dioxaspiro[4.5]dec-7-yl)-2*H*-1,3-benzoxazin-2-one (**1s**).

The preparation of 1,4-dioxaspiro[4.5]decan-6-one was effected by refluxing 22.4 g. (0.2 mole) of 1,2-cyclohexanedione, 12.2 g. (0.2 mole) of ethylene glycol and 0.01 g. of 4-methylbenzenesulfonic acid monohydrate in 150 ml. of benzene under azeotropic conditions for 3 hours. After the solvent was removed, the oily residue was fractionally distilled *in vacuo*. The first fraction (3.1 g.), boiling at 80-105°/40 mm, was discarded. The second fraction, containing 11.2 g. and boiling at 104-105°/18 mm still contained some of the diketone. A third fraction (12.0 g., 38% yield), boiling at 113-115°/16 mm, contained analytically pure, colorless liquid; ir (chloroform); 1730 (C=O), 1203, 1105, 1035 (-O-) cm^{-1}.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75; O, 30.73. Found: C, 61.48; H, 7.76; O, 30.90.

A solution of 5.34 g. (0.03 mole) of 3,4-dihydro-4-hydroxy-3-methyl-2*H*-1,3-benzoxazin-2-one (**4a**), 4.2 g. (0.03 mole) of the above ketone-ketal and 0.02 g. of 4-methylbenzenesulfonic acid monohydrate in 120 ml. of benzene was refluxed 90 minutes while 0.54 ml. of water had separated. After the solvent was removed, the residue was crystallized from acetonitrile giving 5.4 g. (57% yield) of 3,4-dihydro-3-methyl-4-(6-oxo-1,4-dioxaspiro[4.5]dec-7-yl)-2*H*-1,3-benzoxazin-2-one **1s** as white crystals, m.p. 199-200°, dec. An analytical sample was obtained by recrystallization from 2-propanol, m.p. 201-202° dec.; uv λ max (ethanol): nm (ε) 267 (1050), 273 (1000); ir (chloroform): 1721 (OCON), 1708 (ketone C=O); pmr (deuteriochloroform): δ 3.15 (3H, N-CH_3), 4.13 (4H, m, ethylene ketal), 5.25 (1H, d, J = 3.0 Hz, ArC*H*) ppm.

1,2-Dihydro-2-methyl-1-(2-oxopropyl)-3*H*-naphth[1,2-*e*][1,3]oxazin-3-one (**1u**).

A solution of 10.0 g. (0.0437 mole) of 1,2-dihydro-1-hydroxy-2-methyl-3*H*-naphth[1,2-*e*][1,3]oxazin-3-one (**4c**, naphthyl homologue, R_1, R_2 = 5,6  , 2), 40 ml. of acetone, and 0.01 g. 4-methylbenzene sulfonic acid monohydrate in 350 ml. of dry benzene was refluxed for 2 hours while 0.7 ml. of water separated in a Dean-Stark trap. The solvent was removed *in vacuo*. The residue was taken up with 150 ml. of isopropyl ether and refluxed 1 hour to give 8.4 g. of greenish colored crystals, m.p. 123-124°. Concentration of the mother liquor to a low volume gave 1.6 g. of an additional product (total yield, 85%), m.p. 123-124°. Recrystallization from ethyl acetate-isopropyl ether (1:2) gave analytically pure white crystals of **1u**, m.p. 123-124°; uv λ max (ethanol): nm (ε) 228, (65,300), 255 sh (3000), 266 sh (4200), 276 (5000), 280-287 plateau (4000), 308 (1200), 322 (1600); ir (nujol): 1726 (C=O) cm^{-1}.

1,2-Dihydro-2-methyl-1-(2-oxocyclohexyl)-3*H*-naphth[1,2-*e*][1,3]oxazin-3-one (**1v**).

A solution of 20.0 g. (0.088 mole) of 1,2-dihydro-1-hydroxy-2-methyl-3*H*-naphth[1,2-*e*][1,3]oxazin-3-one (**4c**), 10.3 g. (0.105 mole) of cyclohexanone, and 0.005 g. of 4-methylbenzenesulfonic acid monohydrate in 400 ml. of dry benzene was refluxed for 1.5 hours while 1.55 ml. of water separated in a Dean-Stark trap. After the solvent was removed *in vacuo*, the residue was refluxed with 120 ml. of isopropyl ether to give 22.3 g. (82% yield) of white crystals, m.p. 193-194°. Recrystallization from ethyl acetate gave analytically pure **1v**, m.p. 194-195°; uv λ max (ethanol): nm (ε) 268 sh (4350), 274 slv (5200), 277 (5450), 284 (4520), 288 (4420), 309 (1300), 315 (1000), 323 (1750); ir (nujol): 1717, 1691 (C=O) cm^{-1}.

1,1'-(2-Oxo-1,3-cyclohexanediyl)bis[1,2-dihdyro-2-methyl-3*H*-naphth-[1,2-*e*][1,3]oxazin-3-one (**1w** and **1x**).

A solution of 6.0 g. (0.02 mole) of 1,2-dihydro-2-methyl-1-(2-oxocyclohexyl)-3*H*-naphth[1,2-*e*][1,3]oxazin-3-one (**1v**), 4.5 g. (0.02 mole) of 1,2-dihydro-1-hydroxy-2-methyl-3*H*-naphth[1,2-*e*][1,3]oxazin-3-one (**4c**) and 0.01 g. of 4-methylbenzenesulfonic acid monohydrate in 400 ml. of benzene and 100 ml. of tetrahydrofuran was heated to the boiling point and concentrated to *ca.* 440 ml. (whereby most of tetrahydrofuran was removed). On further refluxing for 1 hour, 0.36 ml. of water was collected and the tlc (benzene:acetone:heptane, 3:2:1) showed absence of the starting material **1v** (R_f = 0.45). The new product consisted of two spots, R_f = 0.35 (*ca.* 30%) and R_f = 0.3 (*ca.* 70%). The solution was concentrated to *ca.* 100 ml. to give, on cooling, 4.6 g. (45% yield) of analytically pure, white crystals of *trans*-isomer **1w** (R_f = 0.3), m.p. 281-282°, dec. The filtrate was evaporated to dryness and crystallized from tetrahydrofuran-acetonitrile (1:2) giving 1.1 g. of additional *trans*-isomer (R_f = 0.3, total yield: 56%), m.p. 281-282°, dec.; uv λ max (ethanol): nm (ε) 267 sh (8320), 277 (10,720), 284 (9250), 289 (9300), 310 (2850), 323 (3850); ir (chloroform): 1722 (OCON), 1714 (ketone C=O) cm^{-1}; pmr (deuteriochloroform): δ 3.01 (N-C*H*$_3$), 3.26 (N-C*H*$_3$), 5.60 (1H, d, J = 4.0 Hz, ArC*H*), 5.93 (1H, s, ArC*H*) ppm.

The mother liquor was evaporated to dryness and the residue was crystallized from acetonitrile giving 1.9 g. (19% yield) of analytically and chromatographically (R_f = 0.35) pure *cis*-isomer **1x**, also melting at 281-282° dec.; pmr (deuteriochloroform): δ 3.05 (both *N*-methyls resonate at the same field), 6.07 [2H, s, (ArC*H*)$_2$] ppm. The ultraviolet and infrared spectra of both isomers are practically identical. However, a mixture m.p. gives considerable depression (260-262° dec.).

1,2-Dihydro-2-methyl-1-(1-methyl-4-oxo-3-piperidinyl)-3*H*-naphth[1,3]-oxazin-3-one, Monohydrochloride (**1y**).

To a solution of 10.0 g. (0.044 mole) of 1,2-dihydro-1-hydroxy-2-methyl-3*H*-naphth[1,2-*e*][1,3]oxazin-3-one (**4c**) and 5.0 g. of 1-methyl-4-piperidinone in 75 ml. of anhydrous *N,N*-dimethylformamide was introduced dry hydrogen chloride to *p*H 1.0 at 60° and allowed to stand at room temperature for 24 hours. The solvent was removed *in vacuo* at 60°, and the residue was refluxed with 50 ml. of acetonitrile for 30 minutes to give, on cooling, 11.6 g. of white crystals, m.p. 237-238° dec. Concentration of the mother liquor to *ca.* 15 ml. gave 1.3 g. of additional material (total yield, 81%), m.p. 236-238° dec. An analytically pure product **1y**, melting at 241-242° dec.; was obtained by the recrystallization from acetonitrile; uv λ max (ethanol): nm (ε) 229.5 (69,500), 255 sh (1300), 265-270 plateau (4500), 273-278 plateau (5300), 289 sh (4400), 323 (1700); ir (nujol): 1728, 1708 (C=O) cm^{-1}.

A free base of the above hydrochloride was obtained by treating it with aqueous ammonia at 0° and extracting into ethyl acetate. Drying of the extract with sodium sulfate and concentration to a low volume gave pure product as white crystals, m.p. 162-163° dec.; uv λ max (ethanol): nm (ε) 229 (69,000), 276 (5200), 289 sh (4200), 323 (1800); ir (nujol): 1727 (OCON), 1708 (ketone C=O) cm^{-1}.

Tetrahydro-4-(2-hydroxyphenyl)-3,6-dimethyl-2*H*-1,3-oxazin-2-one (**3a** Table IIIa).

A mixture of 2.0 g. of 3,4-dihydro-3-methyl-4-(2-oxopropyl)-2*H*-1,3-benzoxazin-2-one (2) and 0.8 g. of potassium borohydride in 25 ml. of methanol was stirred at room temperature until a clear solution resulted. After the solution was allowed to stand for two hours at room temperature, the solvent was removed at 28° *in vacuo*. The residue was taken up with water and extracted twice with 25 ml. of ethyl acetate. The combined extracts were dried over sodium sulfate and concentrated to a low volume to give, on cooling, 1.5 g. (75% yield) of off-white crystals, m.p. 244-246°. Recrystallization from ethyl acetate gave analytically pure, white crystals, m.p. 145.5-147°; uv λ max (ethanol): nm (ε) 215 (7400), 274 (2870), 280 sh (2550); ir (nujol): 3050 (OH) 1665 (C=O), 1252 (-O-C=O) cm^{-1}; pmr (DMSO-d_6): δ 1.14 (3H, d, J = 6.5 Hz, C*H*$_3$), 1.94 (2H, m, C*H*$_2$), 2.70 (3H, NC*H*$_3$), 4.07 (1H, q, J = 6.5 Hz, C*H*O), 4.65 (1H, t, J = 3.5 Hz, N-C-*H*), 9.67 (1H, deuterium oxide-exchangeable, phenolic proton) ppm.

Tetrahydro-5-(1-hydroxyethyl)-4-(2-hydroxyphenyl)-3,6-dimethyl-2*H*-1,3-oxazin-2-one (**3c**).

A mixture of 7.8 g. (0.03 mole) of 3-(3,4-dihydro-3-methyl-2-oxo-2*H*-1,3-benzoxazin-4-yl)-2,4-dioxopentane (**1a**) (2), and 2.5 g. of potassium borohydride in 100 ml. of absolute methanol was stirred for 4 hours. Acetic acid was added to the resulting solution at 10° to *p*H 6.0 and the solution was evaporated *in vacuo* at 28°. The residue was taken up with cold water and extracted twice with 100 ml. of ethyl acetate. The combined extracts were dried over sodium sulfate and concentrated to a low volume giving 4.6 g. (60% yield) of phenolic alcoholic product **3c** of analytical purity, m.p. 191-192° dec.; uv λ max (ethanol): nm (ε) 277 (2800); ir (nujol): 3500, 3100 (OH), 1659 (OCON) cm^{-1}; ir (chloroform): 3620, 3300 (OH), 1681 (OCON) cm^{-1}.

5-[1-(Acetyloxy)ethyl]-4-[2-(acetyloxy)phenyl]tetrahydro-3,6-dimethyl-2*H*-1,3-oxazin-2-one (**3d**).

To a solution of 1.0 g. of tetrahydro-5-(1-hydroxyethyl)-4-(2-hydroxyphenyl)-3,6-dimethyl-2*H*-1,3-oxazin-2-one (**3c**) containing 5 drops of triethylamine in 50 ml. of ethyl acetate was added 3 ml. of acetic anhydride and allowed to stand for 2 days at 25°. Cold water was added and stirred 30 minutes followed by the addition of sodium bicarbonate to *p*H 8.0. The two layers were separated, the aqueous phase was washed, dried over sodium sulfate and evaporated to dryness *in vacuo*. Crystallization of the residue from ether gave 0.8 g. (60% yield) of diacetate ester **3d** of analytical purity, m.p. 158-159°; uv λ max (ethanol): nm (ε) 263 (1400), 270 (1200); ir (nujol): 1767 (ArOCOCH$_3$), 1739 (C-OCOCH$_3$), 1698 (OCON) cm^{-1}; pmr (deuteriochloroform): δ 1.25 (3H, d, J = 7.0 Hz, C*H*$_3$CH), 1.59 (1H, J = 7.0 Hz, C*H*$_3$CH), 1.60 (3H, s, OCOC*H*$_3$), 2.38 (4H, OCOC*H*$_3$ and C-C-*H*), 4.52 [2H, m (CH$_3$COO-C*H*$_2$)], 5.11 (1H, d, J = 7.0 Hz) ppm.

Tetrahydro-4-(2-hydroxy-1-naphthalenyl)-3,6-dimethyl-2*H*-1,3-oxazin-2-one (**3e**).

A mixture of 5.4 g. (0.02 mole) of 1,2-dihydro-2-methyl-1-(2-oxopropyl)-3*H*-naphth[1,2-*e*][1,3]oxazin-3-one (**1u**) and 1.0 g. of potassium borohydride in 75 ml. of dry methanol was stirred at 25° for 20 hours. The solvent was removed *in vacuo* at 30° the residue was taken up with cold water and extracted twice with 75 ml. of ethyl acetate. The combined extracts were washed, dried over sodium sulfate and evaporated to dryness *in vacuo*. Crystallization of the residue from acetonitrile gave 3.4 g. (65% yield) of **3e** as white crystals, m.p. 216-217° dec.; uv λ max (ethanol): nm (ε) 231 (65,000), 270 (1800), 280 (2100), 292 (1900), 338 (1000); ir (chloroform): 3180 (OH), 1658 (C=O) cm^{-1}; (nujol): 3150-3050 (OH), 1678 (C=O) cm^{-1}; pmr (DMSO-d_6): δ 1.24 (3H, d, J = 6.5 Hz, C-C*H*$_3$), 2.13 (2H, t, J = 6.5 Hz C*H*$_2$), 2.62 (3H, N-C*H*$_3$), 4.44 (1H, q, J = 6.5 Hz, C*H*CH$_3$), 5.30 (1H, t, J = 6.5, Ar-C*H*), 9.92 (1H, deuterium oxide-exchangeable aromatic OH) ppm.

Octahydro-4-(2-hydroxyphenyl)-3-methyl-2*H*-1,3-benzoxazin-2-one (**3f**, Table IIIb).

A mixture of 6.0 g. (0.023 mole) of 3,4-dihydro-3-methyl-4-(2-oxocyclohexyl)-2*H*-1,3-benzoxazin-2-one (**1b**) (2), in 100 ml. of absolute methanol was stirred 30 minutes and the resulting clear solution was allowed to stand at room temperature overnight. The solvent was removed *in vacuo* at 28°, the residue was taken up with cold water and the white crystalline solid (5.3 g., m.p. 247-249° dec.) was collected by filtration. Recrystallization from 2-propanol-tetrahydrofuran (1:1) gave 3.9 g. (65% yield) of **3f**, m.p. 259-260° dec.; uv λ max (ethanol): nm (ε) 215 (1450), 274 (580); ir (nujol): 3230 (OH), 1673 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 1.20-2.10 (9H, broad envelope, cyclohexane moiety), 2.76 (3H, C*H*$_3$), 4.27 (1H, m, C*H*OH), 4.41 (1H, N-C*H*), 9.84 (1H, deuterium oxide-exchangeable, phenolic proton) ppm.

4-[2-(Acetyloxy)phenyl]-octahydro-3-methyl-2*H*-1,3-benzoxazin-2-one (**3g**).

A solution of 2.6 g. of octahydro-4-(2-hydroxyphenyl)-3-methyl-2*H*-1,3-

benzoxazin-2-one (**3f**), 6 ml. of acetic anhydride and 3 drops of triethylamine in 100 ml. of ethyl acetate was allowed to stand for 4 days at room temperature. Ice-cold water was added and stirred to destroy excess anhydride. The mixture was made basic with ammonium hydroxide, washed and separated. The organic phase was dried over sodium sulfate and concentrated to about 20 ml. to give, on cooling, 1.3 g. of analytically pure acetate ester **3g**., m.p. 200-201° dec. Further concentration of the mother liquor gave 0.9 g. (total yield, 76%) of additional product, m.p. 200-201° dec.; uv λ max (ethanol): nm (ε) 261 (300), 268 (240); ir (nujol): 1680 (N-C(=O)-O), 1766 (ArO-C(=O)-CH$_3$) cm^{-1}; pmr (deuteriochloroform): δ 1.20-2.15 (9H, m. broad envelope of cyclohexane moiety), 2.34 (3H, C*H*$_3$C=O), 2.84 (3H, N-C*H*$_3$), 4.24 (1H, s, Ar-C*H*), 4.41 (1H, m, (C*H*O-C=O) ppm.

Octahydro-4-(2-hydroxyphenyl)-3-methylcyclopent[*e*]-1,3-oxazin-2-one (**3h**).

A mixture of 7.2 g. (0.029 mole) of 3,4-dihydro-3-methyl-4-(2-oxocyclopentyl)-2*H*-1,3-benzoxazin-2-one (**1c**) and 1.0 g. of potassium borohydride in 75 ml. of absolute methanol was stirred for 2 hours and the resulting clear solution was allowed to stand overnight at room temperature. Glacial acetic acid was added to *p*H 6.0 and the solution was evaporated *in vacuo*. The residue was taken up with cold water and extracted twice with 75 ml. of ethyl acetate. The combined extracts were dried over sodium sulfate and concentrated to a low volume giving 4.2 g. (59% yield) of pure product **3h** as white crystals, m.p. 229-230° dec.; uv λ max (ethanol): nm (ε) 217 (7250), 277 (2600); ir (chloroform): 3220 (OH), 1660 (-OCON) cm^{-1}; pmr (deuteriochloroform): δ 1.40-2.10 (7H, broad envelope of cyclopentane moiety), 2.92 (3H, N-C*H*$_3$), 4.55 (1H, m, C*H*O), 4.73 (ArC*H*), 8.23 (1H, deuterium oxide-exchangeable, phenolic OH) ppm.

Octahydro-4-(2-hydroxyphenyl)-3,8-dimethyl-2*H*-1,3-benzoxazin-2-one (**3j**, Table IIIb).

A mixture of 11.0 g. (0.04 mole) of 3,4-dihydro-3-methyl-4-(3-methyl-2-oxocyclohexyl)-2*H*-1,3-benzoxazin-2-one (**1g**) and 2.0 g. of potassium borohydride in 120 ml. of absolute methanol was stirred for 15 minutes and the resulting clear solution was allowed to stand for another 45 minutes at room temperature. The tlc (acetone, benzene, heptane, 3:2:1) showed absence of the starting **1g** (R_f = 0.55) and presence of two new products at R_f = 0.4 (*ca.* 25%) and R_f = 0.35 (*ca.* 75%), respectively. The solution was adjusted to *p*H 6.0 with glacial acetic acid and evaporated to dryness *in vacuo*. The residue was taken up with cold water and extracted twice with 200 ml. of chloroform. The combined extracts were washed, dried over sodium sulfate and the solvent removed. Trituration with hot acetonitrile and cooling gave 5.9 g. (53% yield) of octahydro-4-(2-hydroxyphenyl)-3,8-dimethyl-2*H*-1,3-benzoxazin-2-one (**3j**), chromatographically pure, slower moving rearranged isomer (R_f = 0.35), m.p. 258-259° dec. An analytically pure sample, m.p. 260-261° dec.; was obtained by recrystallization from 2-propanol; uv λ max (ethanol): nm (ε) 216 (1450), 274 (600); ir (nujol): 3250 (OH), 1675 (C=O) cm^{-1}; pmr (DMSO-d$_6$): δ 0.95 (3H, d, J = 6.0 Hz, C-C*H*$_3$), 2.78 (3H, N-C*H*$_3$), 4.04 (1H, C*H*O), 4.40 (1H, ArC*H*), 9.72 (1H, deuterium oxide-exchangeable, phenolic OH) ppm.

4-(2-Hydroxy-3-methylcyclohexyl)-3,4-dihydro-3-methyl-2*H*-1,3-benzoxazin-2-one (**2a**, Table II).

The original mother liquor from the rearranged product **3j** (5.9 g.) containing about 70% of the faster moving isomer (R_f = 0.4), was evaporated to dryness and crystallized from minimum amount of ethyl acetate to give 1.1 g. of additional **3j**, m.p. 248-251° dec. The mother liquor, containing now about 97% of the faster moving product, was concentrated to a low volume giving 1.6 g. (14.5%) of analytically and chromatographically pure (R_f = 0.4) secondary alcohol **2a**, m.p. 155-156°, uv λ max (ethanol): nm (ε) 265 (1000), 272 (900); ir (nujol): 3430 (OH), 1706 (OCON) cm^{-1}; ir (chloroform): 3610, 3430, (OH), 1721, 1708 (OCON) cm^{-1}; pmr (deuteriochloroform): δ 0.95 (3H, d, J = 7.5 Hz, C-C*H*$_3$), 1.80 (OH, deuterium oxide-exchangeable), 3.24 (3H, N-C*H*$_3$), 3.80 (1H, m, C*H*O), 4.22 (1H, d, J = 7.5, ArC*H*) ppm.

Octahydro-3,8-dimethyl-4-{2-[(methylamino)carbonyl]oxy]phenyl}-2*H*-1,3-benzoxazin-2-one (**3k**).

A solution of 1.9 g. (0.007 mole) of octahydro-4-(2-hydroxyphenyl)-3,8-dimethyl-2*H*-1,3-benzoxazin-2-one (**3j**), 1.0 g. of methyl isocyanate and 5 drops of triethylamine in 50 ml. of ethyl acetate was allowed to stand at room temperature for three days. The solvent and excess isocyanate were removed *in vacuo*, and the residue was crystallized from 2-propanol giving 1.6 g. (69% yield) of pure carbamate **3k** as white crystals, m.p. 223-224° dec.; uv λ max (ethanol): nm (ε) 264 (450), 270 (390); ir (nujol): 3230 (NH), 1742 (CH$_3$NHC=O), 1672 (oxazine OCON) cm^{-1}.

4-(5-Chloro-2-hydroxyphenyl)octahydro-3-methyl-2-oxo-2*H*-1,3-benzoxazin-8-propanenitrile (**3l**, Table IIIb).

A mixture of 10.3 g. (0.03 mole) of 3-(6-chloro-3,4-dihydro-3-methyl-2-oxo-2*H*-1,3-benzoxazin-4-yl)-2-oxocyclohexanepropanenitrile (**1k**) and 3.0 g. of potassium borohydride in 200 ml. of absolute methanol was stirred over a period of 1 hour at room temperature. The tlc (acetone, benzene, heptane, 2:2:1) showed absence of starting material (**1k**) and presence of two new products at R_f = 0.3 (*ca.* 75%) and R_f = 0.4 (*ca.* 25%). The solution was adjusted to *p*H 6.0 at 10° with glacial acetic acid and evaporated to dryness *in vacuo*. The residue was taken up with cold water and extracted twice with 200 ml. of ethyl acetate. The combined exctracts were washed, dried over sodium sulfate and concentrated to about 60 ml. to give 5.6 g. (54% yield) of analytically and chromatographically pure 4-(5-chloro-2-hydroxyphenyl)octahydro-3-methyl-2-oxo-2*H*-1,3-benzoxazin-8-propanenitrile (**3l**) as white crystals (R_f = 0.3), m.p. 208-209° dec.; uv λ max (ethanol): nm (ε) 288 (7900), 285 (2850); ir (nujol): 3170 (OH), 2280 (CN), 1660 (OCON) cm^{-1}; pmr (deuteriochloroform): δ 2.85 (3H, N-C*H*$_3$), 4.05, (1H, d, J = 4.5, CH$_3$-N-C*H*), 4.53 (1H, m, C*H*O), 8.91 (1H, deuterium oxide-exchangeable, phenolic OH) ppm.

3-(6-Chloro-3,4-dihydro-3-methyl-2-oxo-2*H*-1,3-benzoxazin-4-yl)-2-hydroxycyclohexanepropanenitrile (**2d**, Table II).

Further concentration of the filtrate of the rearranged product **3l** to a low volume (*ca.* 30 ml.) and cooling gave 2.7 g. of white crystals having *ca.* 95% of the faster moving material (R_f = 0.4), m.p. 196-198°. Recrystallization from ethyl acetate gave 1.6 g. (15.5% yield) of analytically and chromatographically (R_f = 0.4) pure secondary alcohol **2d**, m.p. 200-201°; uv λ max (ethanol): nm (ε) 224 (7300), 274 (1200), 281 (1100); ir (nujol): 3400 (OH), 2280 (CN), 1708 (OCON) cm^{-1}; ir (chloroform): 3620, 3480 (OH), 2300 (CN), 1723 (OCON) cm^{-1}; pmr (deuteriochloroform): δ 3.17 (3H, N-C*H*$_3$), 3.60 (1H, C*H*-O), 4.21 (1H, d, J = 6.5, ArC*H*) ppm.

4,4'-(2-Hydroxy-1,3-cyclohexanediyl)bis[3,4-dihydro-3-methyl-2*H*-1,3-benzoxazin-2-one] (**2e**).

A mixture of 8.4 g. (0.02 mole) of **1f** and 2.0 g. of potassium borohydride in 200 ml. of methanol was stirred at room temperature for 2 hours. Although the solution was never complete, the white copious precipitate which was separating was different from the original mixture. The solid was collected and washed with methanol giving 3.8 g. of secondary alcohol, 4,4'-(2-hydroxy-1,3-cyclohexanediyl)bis[3,4-dihydro-3-methyl-2*H*-1,3-benzoxazin-2-one] (**2e**), m.p. 278-279° dec. The tlc (acetone, benzene, heptane, 2:2:1) showed about 97% purity (R_f = 0.35). Recrystallization from acetonitrile-tetrahydrofuran (2:1) gave 3.2 g. (38% yield) of analytically and chromatographically (R_f = 0.35) pure alcohol **2e**, m.p. 281-282° dec.; uv λ max (ethanol): nm (ε) 267 (2200), 273 (2100); ir (nujol): 3400 (OH), 1708 (OCON) cm^{-1}; pmr (DMSO-d$_6$): 2.95 (3H, N-C*H*$_3$), 3.18 (3H, N-C*H*$_3$), 3.82 (1H, m, C*H*O), 4.70 [2H, m, (ArC*H*)$_2$], 5.21 (1H, d, J = 6.0 Hz, deuterium oxide-exchangeable, OH) ppm.

3,3',4,4',4a',5',6',7',8',8a'-Decahydro-4'-(2-hydroxyphenyl)-3,3'-dimethyl-[4,8'-bi-2*H*-1,3-benzoxazine]-2,2'-dione (**3n**).

To the filtrate of the original solid (3.8 g.) was added glacial acetic acid to *p*H 5.5 and the solution was evaporated *in vacuo*. The residue was taken up with cold water and extracted twice with 200 ml. of ethyl acetate. The combined extracts were washed, dried over sodium sulfate and concentrated to *ca.* 50 ml. After standing in refrigerator overnight,

1.9 g. (23% yield) of analytically and chromatographically (R_f = 0.2) pure rearranged product **3n** was obtained, m.p. 296-297°, dec. Concentration of the mother liquor to a low volume and cooling gave 0.7 g. of additional (total yield, 31%), m.p. 295-296° dec.; ir (nujol): 3380, 3100 (OH), 1703 (benzoxazine OCON), 1660 (oxazine OCON) cm^{-1}; pmr (DMSO-d_6): δ 2.60 (N-C*H*$_3$), 2.76 (N-C*H*$_3$), 3.89 (1H, m, C*H*O), 4.65 [2H, m, (ArC*H*)$_2$], 9.56 (1H, deuterium oxide-exchangeable, phenolic OH) ppm.

6-Chloro-3,4-dihydro-4-(6-hydroxy-1,4-dioxaspiro[4.5]dec.-7-yl)-3-methyl-2*H*-1,3-benzoxazin-2-one (**2f**, Table II).

Potassium borohydride (0.2 g.) was added to a stirred solution of 0.6 g. of 6-chloro-3,4-dihydro-3-methyl-4-(6-oxo-1,4-dioxaspiro[4.5]dec-7-yl]-2*H*-1,3-benzoxazin-2-one (**1t**) in 25 ml. of methanol and the resulting solution was allowed to stand for 1 hour at room temperature. The tlc (acetone, benzene, heptane, 3:2:1) showed absence of the starting material (R_f = 0.5) and the presence of two new spots at R_f = 0.4 (*ca.* 90%) and R_f = 0.25 (*ca.* 10%), respectively. Glacial acetic acid was added to *p*H 6.0 and the solution was evaporated to dryness *in vacuo*. The residue was taken up with water and extracted with 75 ml. of ethyl acetate. The extract was washed, dried over sodium sulfate and concentrated to about 15 ml. to give 0.4 g. (67% yield) of analytically and chromatographically pure (R_f = 0.4) ketal alcohol derivative **2f**, m.p. 219-220°; uv λ max (ethanol): nm (ε) 224 (9050), 273 (2600), 281 (1500); ir (nujol): 3420 (OH), 1713 (OCON) cm^{-1}; ir (chloroform): 3615, 3430 (OH), 1726 (OCON) cm^{-1}; pmr (deuteriochloroform): δ 2.32 (OH, deuterium oxide-exchangeable), 3.18 (N-C*H*$_3$), 3.53 (1H, C*H*O), 3.90 (4H, s, C*H*$_2$-O), 4.17 (1H, ArC*H*) ppm.

3,4,4a,5,6,10b-Hexahydro-4-(2-hydroxyphenyl)-3-methyl-2*H*-naphth[2,1-*e*]-1,3-oxazin-2-one (**3o**, Table IIIc).

A mixture of 6.1 g. (0.02 mole) of 3,4-dihydro-3-methyl-4-(1,2,3,4-tetrahydro-1-oxo-2-naphthalenyl)-2*H*-1,3-benzoxazin-2-one (**1p**) and 2.0 g. of potassium borohydride in 175 ml. of absolute ethanol was stirred for 3 hours at 25°. The tlc (acetone, benzene, heptane, 3:2:1) showed new product to migrate slower (R_f = 0.3) than starting **1o** (R_f = 0.5). The solution was treated with glacial acetic acid to *p*H 6.0 and evaporated to dryness *in vacuo*. The residue was taken up with cold water and extracted twice with 100 ml. of ethyl acetate. The filtrate was dried over sodium sulfate and evaporated to dryness *in vacuo*. Crystallization of the residue with acetonitrile gave 4.7 g. (77% yield) of pure **3o** as white crystals, m.p. 272-273° dec.; uv λ max (ethanol): nm (ε) 272 (3150), 280 sh (2700); ir (nujol): 3100 (OH), 1660 (OCON) cm^{-1}; pmr (DMSO-d_6): δ 4.55 (1H, s, C*H*O), 4.90 (1H, d, J = 3.5 Hz, Ar-C*H*), 9.76 (1H, phenolic OH) ppm.

4-(5-Chloro-2-hydroxyphenyl)-3,4,4a,5,6,10b-hexahydro-8-methoxy-3-methyl-2*H*-naphth[2,1-*e*]-1,3-oxazin-2-one (**3q**).

A mixture of 12.0 g. (0.0322 mole) of 6-chloro-3,4-dihydro-3-methyl-4-(1,2,3,4-tetrahydro-6-methoxy-1-oxo-2-naphthyl)-2*H*-1,3-benzoxazin-2-one (**1r**) and 4.0 g. of potassium borohydride in 200 ml. of absolute methanol was stirred at room temperature for 2 hours. The tlc (acetone:benzene: heptane, 2:2:1) showed complete conversion, the new product having slower mobility (R_f = 0.3) than the starting **1r** (R_f = 0.5). Glacial acetic acid was added to *p*H 6.0 and the solution was evaporated to dryness *in vacuo*. The solid residue was taken up with cold water, stirred 1 hour and filtered. Crystallization from tetrahydrofuran gave 9.1 g. (76% yield) of white crystalline product **3q**, m.p. 279-280° dec. An analytical sample, melting at 283-284° dec.; was obtained by recrystallization from tetrahydrofuran-methanol; uv λ max (ethanol): nm (ε) 227 (21,250), 282 (4480); ir (nujol): 3100 (OH), 1660 (cyclic carbamate) cm^{-1}; pmr (DMSO-d_6): δ 2.83 (3H, N-C*H*$_3$), 3.73 (3H, OC*H*$_3$) 4.61 (1H, ArC*H*-N), 5.03 (1H, C*H*O), 10.26 (1H, phenolic OH) ppm.

4-[5-Chloro-2-[(methylamino)carbonyl]oxy]phenyl]-3,4,4a,5,6,10b-hexahydro-8-methoxy-3-methyl-2*H*-naphth[2,1-*e*]-1,3-oxazin-2-one (**3r**).

A solution of 4.0 g. (0.0107 mole) of **3q**, 3 ml. of methyl isocyamate and 5 drops of triethylamine in 120 ml. of dry tetrahydrofuran was allowed to stand at room temperature for 3 days. A few drows of ethanol was added to destroy excess isocyamate and the solution was evaporated to dryness *in vacuo*. The solid residue was crystallized from acetonitrile giving 3.1 g. (72% yield) of the carbamate ester **3r**, m.p. 254-255° dec. An analytical sample was recrystallized from ethyl acetate, m.p. 256-257°, dec.; uv λ max (ethanol): nm (ε) 227 (20,200), 281 (3860), 293 sh (2400); ir (nujol): 3280 (NH), 1750 (ArOCONHCH$_3$), 1681 (cyclic carbamate); ir (chloroform): 4500, 3800 (NH), 1750 (Ar-OCONHCH$_3$), 1692 (cyclic carbamate) cm^{-1}.

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