Synthesis of 5-Phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepines and Corresponding 3-Ones

GORDON N. WALKER* AND RONALD TIMOTHY SMITH

Research Department, CIBA Pharmaceutical Company, Division of CIBA Corporation, Summit, New Jersey 07901

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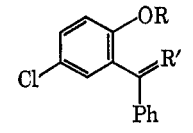
Preliminary, unsuccessful attempts to obtain di- and tetrahydro-5-phenyl-7-chloro-1,4-benzoxazepines through reactions of derivatives of 2-hydroxy-5-chlorobenzophenone oxime (**2a–d**) and of 2-(carboxymethoxy)-5-chlorobenzophenone and benzhydrol (**5–8**) are described. A successful route to the title compounds differing from existing methods for synthesis of (hydro) 1,4-benzoxazepines was found involving novel preparation of *o*-hydroxybenzhydrylamines **11** by reduction of *o*-hydroxybenzophenone imines **10**, O-alkylation with α-halo esters, and thermal closure to lactams **12a**, followed by N-alkylation and hydride reduction to the cyclic amines **13**.

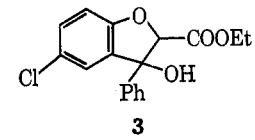
Tetrahydro-5-aryl-1,4-benzoxazepines such as **12** and **13** (Scheme I) might be of pharmacological interest, owing to their structural similarity to the well-known 5-aryl-3*H*-1,4-benzodiazepines.[1,2] Synthetic hydro-1,4-benzoxazepines, prepared starting from salicylaldehydes,[3,4] *o*-hydroxyacetophenones,[5,6] salicylamides with α-halo ketones and α-halo esters,[7] *N*-(*o*-hydroxybenzyl)-anilines,[8] or *o*-hydroxybenzophenones,[9] and tetrahydro-4,1-benzoxazepines, obtained from *o*-aminobenzhydrols,[10] have appeared recently, some of the reports attesting that compounds of this type are not easy to synthesize by classical methods.

Our initial attempts to arrive at **12**, starting from phenolic ketone **1a** and its oxime **2a**, failed for reasons which may be outlined briefly as follows. Diacetyl (**2b**) and chloroacetyl (**1b**, **2c**, **2d**) derivatives were labile, hydrolyzing or aminolyzing back to **1a** or **2a** readily. The carbonyl group of **1a** being relatively inert, **1a** did not condense with glycine ester (pyridine)[1] or ethyl cyanoacetate,[11] and even Perkin condensation giving 4-phenyl-6-chlorocoumarin[12] was difficult. With NaH (toluene) and ethyl bromoacetate, **1a** gave mainly benzofuran **4a** (structure confirmed by spectra and conversion to acid **4b** and amide **4c**) and, as a by-product, corresponding ketol **3**. Milder ethyl bromoacetate alkylation (K_2CO_3) of **1a** gave **5a** which was readily converted to amide **5b** by ammonolysis. Whereas sodium borohydride reduction of **5a** gave diol **6**, further indicating the highly reactive nature of the ester group, reduction of **5b** under the same conditions gave amide carbinol **7a**. This in turn with $SOCl_2$ gave chloroamide **7b**, but no seven-membered lactam could be prepared from **7b** by internal displacement. Products of the reaction of **7b** with sodium methoxide were identified as **8a**, **8b**, and NH_3.

We then sought a relatively facile way to introduce an amino group on the benzhydryl carbon at the onset.



1a, R = H; R′ = O
b, R = $COCH_2Cl$; R′ = O
2a, R = H; R′ = NOH
b, R = $COCH_3$; R′ = $NOCOCH_3$
c, R = $COCH_2Cl$; R′ = $NOCOCH_2Cl$
d, R = H; R′ = $NOCOCH_2Cl$



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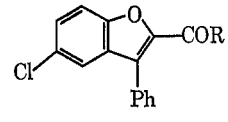
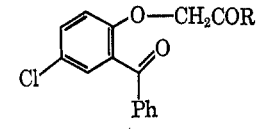
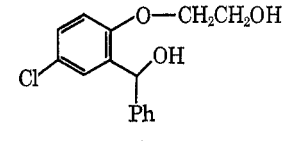


4a, R = OEt
b, R = OH
c, R = NH_2



5a, R = OEt
b, R = NH_2



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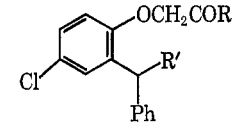

7a, R = NH_2; R′ = OH
b, R = NH_2; R′ = Cl
8a, R = NH_2; R′ = OCH_3
b, R = OH; R′ = OCH_3

o-Hydroxybenzhydrylamines have been reported as products of reduction of *o*-hydroxybenzophenone oximes[13] and 3-arylbenzisoxazoles,[14] and also as Curtius rearrangement products of azides from 3-phenylbenzofuran-2-ones,[15] but these routes do not seem practical for preparative work. On the other hand, although a number of *o*-hydroxy and otherwise substituted benzophenone imines have been prepared from nitriles with ArMgX reagents and their hydrolysis rates studied,[16] they have not been used as benzhydrylamine precursors. We found that *o*-hydroxy imine **10**, a relatively stable, bright yellow, highly chelated substance, could be prepared readily in quantity by action of excess ammonia on **1a** in ethanol. After some preliminary work, in which it was learned that large excesses of strongly

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(15) A. Darapsky, H. Berger, and A. Neuhaus, *J. Prakt. Chem.*, **147**, 145 (1936).
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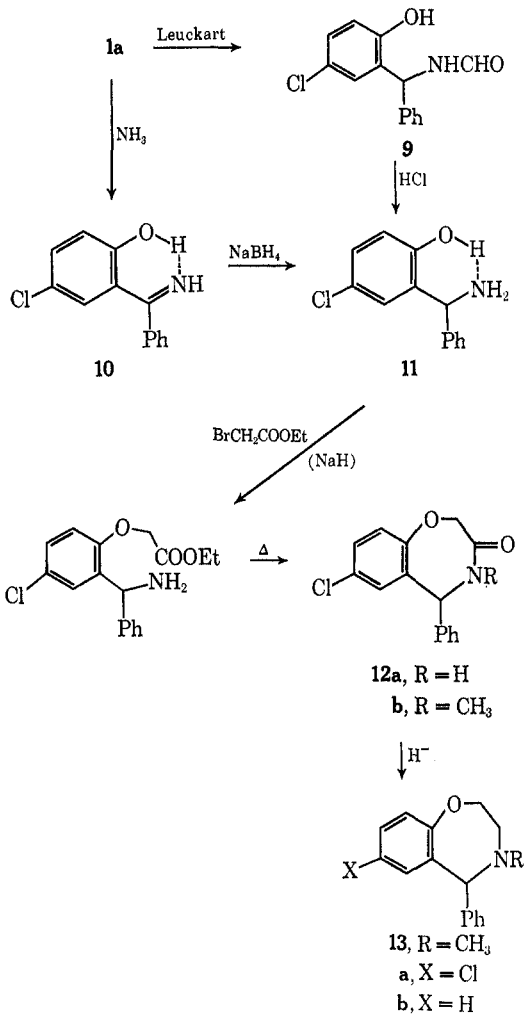
SCHEME I



basic reagents and overly vigorous conditions, leading to loss of NH_3, had to be avoided, it was possible to reduce **10** to the colorless aminophenol **11** with $NaBH_4$ in methanol.[17,18] Compound **11** (·HCl) was also prepared, more arduously, by Leuckart reaction of **1a** and acid hydrolysis of resulting **9**. With **11** in hand, one could try a variety of acylations and alkylations. Although certain acylations of **11** proved to be rather surprisingly complex, alkylations of the preformed phenolate anion were more straightforward. Thus **11** with ethyl bromoacetate (NaH) gave an oily mixture, probably owing to partial N-alkylation, consisting largely of the expected ethoxycarbonylmethoxy amine. This was evident during work-up and subsequent heating of the crude oil, when lactam **12a** crystallized and was isolated readily in 16% yield. In view of Luts' yield of 2.4% of demethyl **13a** from Leuckart reaction of **1** (R = CH_2CH_2Cl; R′ = O), hydrolysis, and closure,[9] these results represent significant improvement in the construction of this ring system.

Infrared and nmr spectra (see Experimental Section) having shown structure **12a** to be correct, further confirmation was adduced by first methylating **12a** to **12b** and reducing **12b** to the cyclic amine **13a** with $LiAlH_4$ in ether. This reduction had to be done gently to retain the chloro substituent, for under more vigorous conditions (refluxing tetrahydrofuran) there was partial dechlorination to give **13b**, also isolated and characterized.

Only moderate hypotensive (and no significant central nervous) effects were observed in pharmacological testing of compounds **12** and **13**.

Experimental Section[19]

2-Hydroxy-5-chlorobenzophenone Oxime (2a).—Refluxing 41.5 g of 2 hydroxy-5-chlorobenzophenone (**1a**) and 20 g of hydroxylamine hydrochloride in 40 ml of pyridine and 250 ml of 90% ethanol (water) for 4 hr, evaporation, treatment with water, and recrystallization from aqueous methanol gave (100%) colorless crystals: mp 144–145.5°; base soluble, ferric chloride positive; ir 2.98, 6.12 μ; uv 276 nm (ε 12,080).

Anal. Calcd for $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66. Found: C, 63.08; H, 4.02; N, 5.66.

The corresponding ***O,O′*-diacetate (2b)**, obtained by heating a sample of the oxime 2 hr with excess acetic anhydride and evaporating, was recrystallized from methanol, mp 119–121°, ir 5.65 μ.

Anal. Calcd for $C_{17}H_{14}ClNO_4$: C, 61.54; H, 4.25; N, 4.22. Found: C, 61.65; H, 4.32; N, 4.07.

The corresponding ***O,O′*-bischloroacetate (2c)** was obtained by warming 2 g of the phenolic oxime with 11 ml of chloroacetyl chloride on steam cone 0.5 hr. The residue, after evaporation and treatment with water, crystallized in the presence of methanol: colorless crystals; mp 142–143.5°; ir doublet 5.59, 5.64 μ; uv 318 nm (ε 3380) and inflection 260 nm (ε 7890); ferric chloride negative.

Anal. Calcd for $C_{17}H_{12}Cl_3NO_4$: C, 50.96; H, 3.02; N, 3.50. Found: C, 51.20; H, 3.09; N, 3.44.

The corresponding **chloroacetyloximinophenol (2d)** was obtained by treating 10 g of the phenolic oxime with 20 ml of chloroacetyl chloride at room temperature. The reaction was nonexothermic, but much HCl was evolved. After standing 1.5 hr the solution was poured into cold water, and the product was collected, washed with water, and triturated with and recrystallized from ethanol to give 6.5 g of colorless crystals: mp 119.5–121°; ir 5.57 μ; uv 317 nm (ε 4150) with inflection 259 nm (ε 7650); ferric chloride positive (purple color).

Anal. Calcd for $C_{15}H_{11}Cl_2NO_3$: C, 55.57; H, 3.42; N, 4.32. Found: C, 55.53; H, 3.53; N, 4.26.

The monochloracetate reverted to the phenolic oxime on treatment with methanolic methylamine or sodium methoxide solutions.

2-(Chloroacetoxy)-5-chlorobenzophenone (1b).—Heating 40 g of **1a** with 100 ml of chloroacetyl chloride at 100° for 2 hr, treatment of the cooled residue with water, and trituration of the resulting crude product with methanol gave 25 g of the recovered phenol and, from the filtrate, 4.5 g of chloroacetate: mp 88–90°, raised on further recrystallization (methanol) to mp 89.5–90.5°; ferric chloride negative; ir 5.63 and 6.01 μ; uv 221, 256, and 345 nm (ε 19,840, 11,770, and 3230, respectively). The chloroacetate reverted easily to the phenol on treatment with bases and gave imine **10** on treatment with ethanolic ammonia.

Anal. Calcd for $C_{15}H_{10}Cl_2O_3$: C, 58.27; H, 3.26. Found: C, 58.50; H, 3.38.

2-Hydroxy-5-chlorobenzhydrol.—A methanol suspension of 4 g of **1a** or its chloroacetate was treated with excess sodium borohydride (*ca.* 10 g) in portions. The solution was heated (steam cone) 10 min, cooled, and treated with water, and the resulting solution acidified with HCl. The colorless oil was extracted with ether, the washed (water) and dried ($MgSO_4$) organic solution evaporated, and the residue recrystallized from cyclohexane, giving colorless crystals: mp 89–90.5°; ir 2.90, 3.10 μ; uv 286 nm (ε 2980).

Anal. Calcd for $C_{13}H_{11}ClO_2$: C, 66.53; H, 4.73. Found: C, 66.41; H, 4.54.

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(19) Melting points were obtained using a Thomas–Hoover silicone oil bath, infrared spectra (Nujol mulls, unless otherwise noted) were recorded with Perkin-Elmer double-beam instrument, ultraviolet curves (methanol solutions) were measured by a Cary recording spectrophotometer, and nmr data were obtained using Varian A-60 60-Mc apparatus with TMS internal standard. We are indebted to Mr. Louis Dorfman, Mr. George Robertson, Mr. Rudolf Oeckinghaus, Miss Ruth Behnke, Mrs. Margaret Mulligan, and Mr. Charles Navarro for analytical and spectral data, and to Mrs. Angela Aretakis for literature search work.

2-Ethoxycarbonyl-3-phenyl-5-chlorobenzofuran (**4a**).—A stirred solution of 13.5 g of **1a** in 200 ml of warm toluene was treated with 2.5 g of 56% NaH (oil) and then 9 ml of ethyl bromoacetate, and the mixture was refluxed and stirred for 5.5 hr. After the mixture was cooled and treated with water, the ether-diluted, washed (water), and dried ($MgSO_4$) organic solution was evaporated to give yellow oil from which **4a** crystallized on standing (4.1 g), and was collected with the aid of a small amount of ethanol and recrystallized from ether: mp 105–106°; ir 5.80 μ; uv 216 and 286 nm (ϵ 29,170 and 15,950).

Anal. Calcd for $C_{17}H_{13}ClO_3$: C, 67.91; H, 4.36. Found: C, 67.92; H, 4.45.

2-Ethoxycarbonyl-3-hydroxy-3-phenyl-5-chloro-2,3-dihydrobenzofuran (**3**) crystallized from the mother liquor after removal of **4a**: crystals from ether; mp 134–137°; ir 2.91 (intense) and 5.77 μ; uv 289 nm (ϵ 3260).

Anal. Calcd for $C_{17}H_{15}ClO_4$: C, 64.05; H, 4.74. Found: C, 64.08; H, 4.71.

Compound **3** gave **4a** on warming with acids or PPA. Compound **4a** was further characterized by hydrolysis (10% sodium hydroxide, 1.5-hr reflux, dilution and acidification) to corresponding acid **4b**, recrystallized from ethanol: mp 254.5–256.5° slow dec; ir 5.95 μ.

Anal. Calcd for $C_{15}H_9ClO_3$: C, 66.07; H, 3.33. Found: C, 66.37; H, 3.50.

The acid was further converted to the corresponding acid chloride ($SOCl_2$) and thence, using concentrated NH_4OH and standard methods, to amide **4c**: crystals from ethanol; mp 186–188°; ir 2.88, 3.01, and 6.01 μ; uv 282 nm (ϵ 14400).

Anal. Calcd for $C_{15}H_{10}ClNO_2$: C, 66.30; H, 3.71; N, 5.16. Found: C, 66.15; H, 3.85; N, 5.27.

2-(Ethoxycarbonylmethoxy)-5-chlorobenzophenone (**5a**).—To a solution of 19.1 g of **1a** in 1400 ml of acetone was added 20 g of ethyl bromoacetate and 18.5 g of anhydrous potassium carbonate. The suspension was refluxed vigorously 7.5 hr and filtered, the filtrate was evaporated, the residue was taken into ether and clarified by another filtration, and the solvent again evaporated, to give crude, oily product. The keto ester was characterized as the 2,4-dinitrophenylhydrazone, red crystals from ethanol, mp 161–163°.

Anal. Calcd for $C_{23}H_{19}ClO_7N_4$: C, 55.37; H, 3.84; N, 11.23. Found: C, 55.61; H, 3.88; N, 11.48.

2-(β-Hydroxyethoxy)-5-chlorobenzhydrol (**6**).—Reduction of *ca.* 12 g of the preceding, crude keto ester **5a** was carried out in methanol with sodium borohydride (*ca.* 8 g) added in portions. After 15-min heating (steam cone) and evaporation of solvent, the cooled residue was treated with water. The colorless, crude product crystallized and was collected, washed with water, dried (yield 5.3 g), and recrystallized from ether: mp 124–125.5°; ir 3.12 μ (very broad, intense).

Anal. Calcd for $C_{15}H_{15}ClO_3$: C, 64.63; H, 5.42. Found: C, 64.82; H, 5.14.

2-Benzoyl-4-chlorophenoxyacetamide (**5b**) was prepared by saturating a solution of *ca.* 18 g of crude keto ester **5a** in 300 ml of ethanol with ammonia. After standing 3 days the alcoholic solution was evaporated, and the syrupy residue with the aid of methanol afforded 4.8 g of crystalline amide. Recrystallization from methanol gave colorless crystals: mp 184–186°; ir 2.90, 5.92 and 6.06 μ; uv 251 nm (ϵ 13,800) with inflection 312 nm (ϵ 2120).

Anal. Calcd for $C_{15}H_{12}ClNO_3$: C, 62.18; H, 4.18; N, 4.84. Found: C, 62.41; H, 4.17; N, 4.70.

2-(α-Hydroxybenzyl)-4-chlorophenoxyacetamide (**7a**) was obtained by sodium borohydride reduction of **5b** (4.5 g), following usual procedure of adding the excess reagent in portions to a methanol solution of the keto amide and thereafter warming 20–30 min on a steam cone and evaporating methanol. After treatment with water, the crude crystals were collected, water-washed, dried, and recrystallized (ether–methanol) to give (4.2 g) colorless crystals: mp 143–145°; ir 2.89, 2.97, 3.06, 3.17, and 5.94 μ; uv 280 nm (ϵ 2190).

Anal. Calcd for $C_{15}H_{14}ClNO_3$: C, 61.75; H, 4.84; N, 4.80. Found: C, 61.71; H, 4.87; N, 4.69.

2-(α-Chlorobenzyl)-4-chlorophenoxyacetamide (**7b**).—On treatment with excess thionyl chloride (50 ml) the hydroxyamide **7a** (2 g) reacted rapidly. The solution was warmed gently 15 min, the excess reagent was removed *in vacuo*, and the residual material was obtained in crystalline form (1.4 g) using ether: colorless crystals; mp 152.5–154.5°; ir 2.92, 3.20, and 5.93 μ; uv 281–287 nm (ϵ 2270).

Anal. Calcd for $C_{15}H_{13}Cl_2NO_2$: C, 58.08; H, 4.22; N, 4.52. Found: C, 57.78; H, 3.99; N, 4.43.

Methyl 2-(α-Methoxybenzyl)-4-chlorophenoxyacetate (**8a**) **and Methoxy Acid** (**8b**).—To a solution of 0.15 g of sodium in 40 ml of methanol was added 1.0 g of **7b**. After refluxing 1 hr, the methanol was evaporated *in vacuo* (NH_3 present, as evidenced by odor) and the cooled residue treated with water. Crystals of **8a** which separated were collected (0.25 g), washed with water, dried, and recrystallized from ether: mp 141–142°; ir 2.89, 3.20, and 5.89 μ; uv 281 nm (ϵ 2370).

Anal. Calcd for $C_{16}H_{16}ClO_3N$: C, 62.85; H, 5.28; N, 4.58. Found: C, 62.74; H, 5.40; N, 4.51.

Acidification (HCl) of the aqueous filtrate gave 0.45 g of **8b**. Recrystallization from ether gave a pure sample: mp 160–162°; ir 5.74–5.83 μ and bonded OH and carboxylate bands; uv 282 nm (ϵ 2420).

Anal. Calcd for $C_{16}H_{15}ClO_4$: C, 62.64; H, 4.93. Found: C, 62.83; H, 5.03.

2-Hydroxy-5-chlorobenzophenone Imine (**10**).—A brisk steam of anhydrous ammonia was passed into an uncooled suspension of 130 g of 2-hydroxy-5-chlorobenzophenone in 1.2 l. of EtOH for 1.8 hr. Within 1 hr the crystals of **1a** had dissolved and product began to separate. After standing overnight the suspension was filtered; the first crop of product, 69 g of orange-yellow crystals, had mp 134–136°, not raised on recrystallization (ethanol). Additional, less pure product (40 g) was obtained after concentrating the ammoniacal solution. The analytical sample, mp 134–136.5° from ethanol, was shiny, yellow flakes: ir 6.25 (sharp), bonded 3.19–3.27, and broad, dipolar bands 3.78–4.33 μ; uv 224, 336–350, and 421 nm (ϵ 18,180, 1220, and 6750, respectively) with inflections 236 and 272 nm. The compound was soluble in 10% hydrochloric acid (solution colorless), and gave strong ferric chloride test and precipitate with cupric acetate.

Anal. Calcd for $C_{13}H_{10}ClNO$: C, 67.39; H, 4.35; N, 6.05. Found: C, 67.09; H, 4.48; N, 6.20.

2-Hydroxy-5-chloro-α-aminodiphenylmethane (**11**).—The imine **10** (69 g) in 300 ml of warm (30°) methanol was treated (stirring) gradually (5 min) with 10–12 g of sodium borohydride, or *ca.* several grams in excess of the amount required to convert from yellow to colorless solution. After warming briefly and gently to ensure breakdown of any excess hydride, the solution was cooled and treated with 2 l. of water, and the crude amine extracted with ether (in some runs it crystallized directly and was collected). The ether solution was washed with water and extracted with 10% hydrochloric acid. The chilled, acid solution was neutralized carefully with cold, concentrated NaOH solution and the amine again either filtered or extracted with ether; the water-washed, dried ($MgSO_4$), and evaporated ether solution gave colorless crystals (44.8 g), mp 135–136° (solvated). Recrystallization from methanol gave a sample: mp 136.5–137.5°; ir 2.98, 3.05 μ and broad, moderately intense band centered *ca.* 4.03 μ, indicative of aminium phenolate form; uv 287 nm (ϵ 2820).

Anal. Calcd for $C_{13}H_{12}ClNO$: C, 66.81; H, 5.18; N, 5.99. Found: C, 67.13; H, 5.29; N, 5.96.

The corresponding hydrochloride, obtained from the aminophenol with alcoholic HCl or from its attempted chloroacetylation, and also from hydrolysis of **9** as described next, was recrystallized from ethanol–ether or methanol–ethyl acetate: colorless crystals; mp 218–220° dec; uv 288 nm (ϵ 3020).

Anal. Calcd for $C_{13}H_{12}ClNO \cdot HCl$: C, 57.79; H, 4.85; N, 5.19. Found: C, 57.57; H, 4.53; N, 5.04.

Both the aminophenol and its hydrochloride gave ferric chloride tests, but whereas that of the salt was blue and relatively permanent, that of the base itself was red and transient, indicating relatively facile oxidation of the benzhydrylamine moiety.

The corresponding *O,N*-**dibenzoate** was prepared by usual Schotten–Baumann method (benzoyl chloride and 5% sodium hydroxide solution) and after recrystallization from cyclohexane had mp 108–111°: ir 3.02, 5.74, 6.10, and 6.54 μ.

Anal. Calcd for $C_{27}H_{20}ClNO_3$: C, 73.38; H, 4.56; N, 3.17. Found: C, 73.60; H, 4.52; N, 3.27.

Other attempted acylations, with, *e.g.*, $ClCH_2COCl$, Ac_2O, AcCl, ClCOOEt, etc., appeared to be quite complex and did not afford crystalline, well-characterized derivatives.

Leuckart Reaction (**9**).—A solution of 20 g of **1a** and 30 g of ammonium formate in 100 ml of formamide and 75 ml of formic acid was distilled slowly until temperature of solution reached 175° and then refluxed 6 hr. The cooled solution was poured into ice water. The crude product was collected, triturated and

washed with water, dried (yield 20.3 g), and recrystallized from ethyl acetate–ether: colorless crystals; mp 169–171°; ir 2.99–3.07 and 6.06–6.12 μ; uv 286 nm (3100).

Anal. Calcd for $C_{14}H_{12}ClNO_2$: C, 64.25; H, 4.62; N, 5.35. Found: C, 64.48; H, 4.89; N, 5.46.

Hydrolysis of **9** (concentrated HCl, 4.5 hr reflux) gave a sample of **11** HCl, identical with that prepared *via* reduction of imine **10**.

5-Phenyl-7-chloro-2,3,4,5-tetrahydro-1,4-benzoxazepin-3-one (12a).—A stirred solution of 25 g of aminophenol **11** in 500 ml of toluene was treated with 4.8 g of 56% sodium hydride (oil) and 5–10 min thereafter with 12.5 ml of ethyl bromoacetate. The suspension was refluxed and stirred 4 hr. The cooled, filtered, and ether-diluted organic solution was washed with three portions of water, dried (K_2CO_3), and partly evaporated. Compound **12a** (2.7 g), crystallized from the solution, and collected and washed with ether, had mp 206–208°. The mother liquor, after evaporation while heating on steam cone, afforded 1.9 g of additional lactam **12a**, mp 204–206°, on trituration with ether, bringing the yield to 4.6 g (15.7%). Recrystallization from methanol gave a pure sample: mp 206.5–208.5°; ir 3.14, 3.27 (moderate), and 6.00 μ (intense); uv 272, 279, and 291 nm (ε 980, 990, and 210, respectively); nmr ($CDCl_3$) δ 7.35–6.9 (m, 8, aromatic protons), 5.71–5.65 (d, 1, benzhydryl proton coupled to NH, collapsed to δ 5.68 s when NH exchanged with D_2O), and 4.57 (s, 2, magnetically equivalent protons at position 2).

Anal. Calcd for $C_{15}H_{12}ClNO_2$: C, 65.82; H, 4.42; N, 5.12. Found: C, 65.93; H, 4.44; N, 4.98.

4-Methyl-5-phenyl-7-chloro-2,3,4,5-tetrahydro-1,4-benzoxazepin-3-one (12b).—Lactam **12a** (3.0 g) in toluene (200 ml) was treated with 1.5 g of 56% sodium hydride (oil) and then 20 ml of iodomethane, and the mixture was stirred and refluxed for 7 hr. After cooling, water treatment, and dilution with ether, the separated, washed (water), dried ($MgSO_4$), and evaporated organic layer afforded 2.8 g of colorless crystals, mp 177–181° (from ether). Recrystallization from methanol gave a sample: mp 180–182°; ir 6.13 μ; uv 280 nm (ε 1220) with inflections 271 nm (ε 1090) and 291 (500); nmr ($CDCl_3$) δ 7.43–6.88 (m, 8, aromatic protons), 5.31 (s, 1, benzhydryl proton), 4.95–4.14 (symmetric AB 1:2:2:1* quartet centered 4.54, J = 16 Hz, magnetically nonequivalent position 2 protons), and 3.28 (s, 3, N-methyl).

Anal. Calcd for $C_{16}H_{14}ClNO_2$: C, 66.78; H, 4.90; N, 4.87. Found: C, 66.51; H, 5.12; N, 4.88.

4-Methyl-5-phenyl-7-chloro-2,3,4,5-tetrahydro-1,4-benzoxazepine (13a).—Reduction of 3.5 g of N-methyllactam **12b** with 4 g of lithium aluminum hydride in 500 ml of ether with 1-hr stirring and reflux, followed by addition of 16 ml of water at 0°, 0.5-hr stirring at 26°, and filtration, gave a solution of crude base which was dried (K_2CO_3) and evaporated: yield 3.5 g of slightly greenish oil; soluble in dilute acids; ir devoid of C=O bands.

The corresponding hydrochloride was precipitated from ether with ethanolic HCl and recrystallized from ethanol–ether: colorless crystals; mp 231–233° dec; ir 4.08 μ (broad, intense); uv 269 nm (ε 940).

Anal. Calcd for $C_{16}H_{16}ClNO \cdot HCl$: C, 61.94; H, 5.53; N, 4.52. Found: C, 61.69; H, 5.66; N, 4.57.

The corresponding picrate was prepared in and recrystallized from ethanol: yellow crystals; mp 201.5–204° dec.

Anal. Calcd for $C_{22}H_{19}ClN_4O_8$: C, 52.54; H, 3.81; N, 11.14. Found: C, 52.84; H, 4.09; N, 11.10.

When 2.0 g of **12b** was reduced with lithium aluminum hydride (5 g) in tetrahydrofuran, and refluxing for 7.5 hr, the crude base (1.4 g) afforded a hydrochloride which, on crystallization from ethanol–ether, was obtained in two fractions, mp 224–228° dec and mp *ca.* 138–150° dec. Clarified, aqueous solutions of the lower melting, more soluble hydrochloride fraction, on dropwise treatment with 10% sodium hydroxide solution, gave amorphous, crude **deschloramine 13b** which, after isolation by ether extraction, drying (K_2CO_3), and evaporation, was also characterized by preparation of salts.

The corresponding hydrochloride, mp 151–155° dec (from ethanol–ether), apparently was a hydrate.

Anal. Calcd for $C_{16}H_{17}NO \cdot HCl \cdot H_2O$: C, 65.41; H, 6.86. Found: C, 65.17; H, 6.90.

The corresponding picrate was recrystallized from ethanol: yellow crystals; mp 190–192°; analytically devoid of chlorine.

Anal. Calcd for $C_{22}H_{20}N_4O_8$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.15; H, 4.49; N, 12.3.

Registry No.—**1b**, 26965-43-5; **2a**, 26965-44-6; **2b**, 27005-98-7; **2c**, 26965-45-7; **2d**, 27005-99-8; **3**, 26965-46-8; **4a**, 27006-00-4; **4b**, 26965-47-9; **4c**, 26965-48-0; **5a** 2,4-DNP, 26965-49-1; **5b**, 26965-50-4; **6**, 26965-51-5; **7a**, 26965-52-6; **7b**, 26965-53-7; **8a**, 26965-54-8; **8b**, 26965-55-9; **9**, 26965-56-0; **10**, 26965-57-1; **11**, 26965-58-2; **11** HCl, 26965-59-3; **11** *O*,*N*-dibenzoate, 26965-60-6; **12a**, 26965-61-7; **12b**, 26965-62-8; **13a** HCl, 26965-63-9; **13a** picrate, 26965-64-0; **13b** HCl, 26965-65-1; **13b** picrate, 26965-66-2; 2-hydroxy-5-chlorobenzhydrol, 26965-67-3.