Quinazolines and 1,4-Benzodiazepines. 55.[1] Synthesis of Two Metabolites of Demoxepam† Isolated from the Dog

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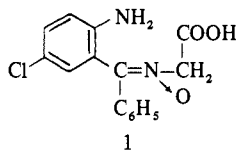
Schwartz, *et al.*,[2] have studied the metabolic disposition of demoxepam† in dogs previously given iv and oral doses of this drug. These workers demonstrated the presence of the open lactam **1**, oxazepam‡ (**2**), the 5-(4′-hydroxyphenyl) derivative **3**, the *N*-desoxy derivative of **3** and two additional phenolic products. Spectral data on the purified metabolites suggested these latter substances to be 7-chloro-9-hydroxy-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**8**) and the corresponding *N*-oxide **9**. We wish to report here the synthesis of compounds **8** and **9** which have been shown[2] to be identical spectrally and by the use of tlc procedures to the two metabolites in question.



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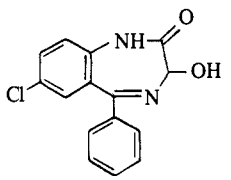

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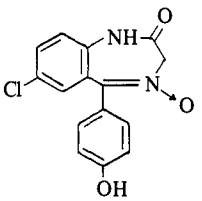

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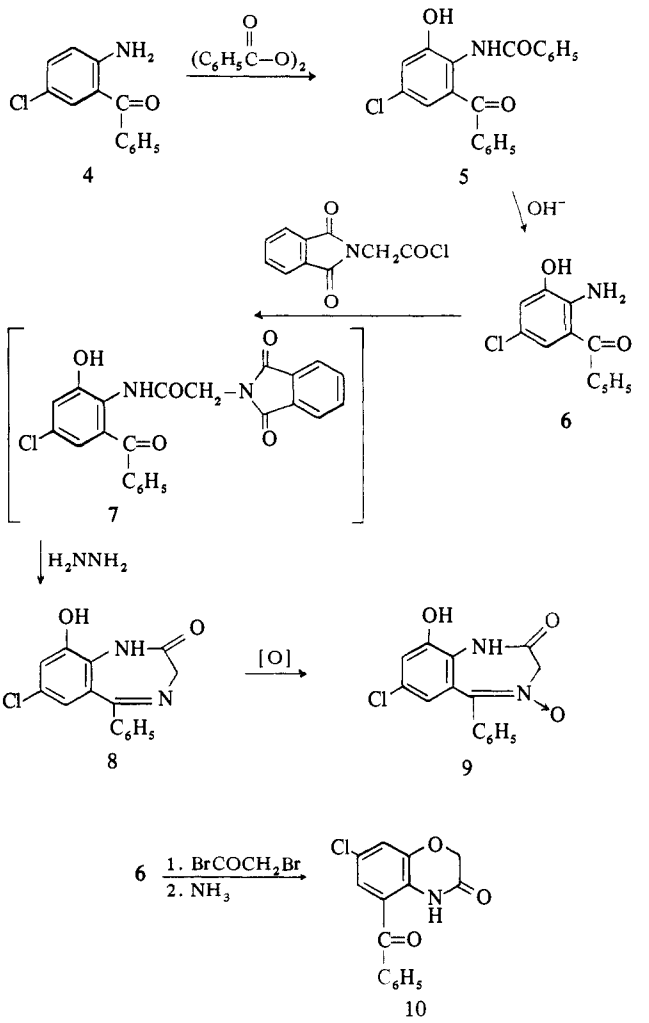
The requisite 2-amino-3-benzoyl-5-chlorophenol (**6**) required for this work was prepared by application of the previously described[3] dibenzoyl peroxide procedure for hydroxylation of simple aniline derivatives to 2-amino-5-chlorobenzophenone (**4**). After alkaline hydrolysis[4] of the intermediate *N*-benzoyl derivative **5**, the desired phenol **6** was obtained in 13% yield. The position of hydroxylation was established by nmr spectroscopy [$(CD_3)_2CO$] in which the product displayed the AB quartet pattern (δ 6.86 and 6.97) and coupling constant (2 Hz) characteristic for meta-coupled hydrogens. Treatment of **6** with bromoacetyl bromide followed by reaction with liquid ammonia gave 5-benzoyl-7-chloro-2*H*-1,4-benzoxazin-3(4*H*)-one (**10**) instead of the desired diazepinone **8**. To avoid this undesired cyclization reaction, acylation was effected with the acid chloride prepared from phthaloylglycine. The resultant protected aminoacetamido derivative **7** upon heating with hydrazine yielded the benzodiazepinone **8** in 38% yield. Oxidation of **8** with *m*-chloroperbenzoic acid gave the *N*-oxide **9** in 70% yield.



4 5 6 7 8 9

10

Experimental Section

All melting points were determined microscopically on a hot stage and are corrected. Ir spectra were determined using a Beckman IR-9 spectrophotometer, nmr spectra with a Varian A-60 spectrometer. Analyses (C, H, N) obtained for compounds reported in this paper were within ±0.4% of theoretical values.

2-Benzoyl-4′-chloro-6′-hydroxybenzanilide (5).§ To a stirred soln of **4** (50 g, 0.215 mole) in 500 ml of C_6H_6, heated in an oil bath at 60–70°, was added a soln of dibenzoyl peroxide (52.2 g, 0.215 mole) in 425 ml of C_6H_6 during 30 min. The soln was stirred and heated at 60–70° for 44 hr. The dark mixture was cooled, treated with 500 ml of satd $NaHCO_3$ soln, and then washed with 2% $NaHCO_3$ (2 × 150 ml). The C_6H_6 layer was then extd with 1 *N* NaOH (3 × 100 ml) and the aqueous layer sepd, washed with Et_2O, and neutralized with concd HCl. The ppt was filtered, washed with H_2O, and air-dried to give 13.7 g (18%) of crude **5**. The product was purified by filtering over Florisil with C_6H_6 to give after evaporation, 11.4 g (15%) of yellow crystals, mp 120–122°. *Anal.* ($C_{20}H_{14}ClNO_3$) C, H, N.

2-Amino-3-benzoyl-5-chlorophenol (6).§ A soln of **5** (21.4 g, 0.06 mole) in 215 ml of 2 *N* NaOH was heated under reflux for 5 hr, cooled, acidified with concd HCl, and extd with CH_2Cl_2. The organic layer was sepd, washed with satd $NaHCO_3$, dried, and concd to give 13.3 g (80%) of **6** as yellow crystals. The analytical sample, mp 166–168°, was prepd by recrystn from EtOH–H_2O. *Anal.* ($C_{13}H_{10}ClNO_2$) C, H, N.

7-Chloro-9-hydroxy-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8). To a stirred suspension of **6** (2.5 g, 0.01 mole) in 40 ml of C_6H_6 was added the acid chloride of phthaloylglycine (2.2 g, 0.01 mole). The mixture was heated under reflux for 30 min. The cooled reaction mixture was filtered and the solid washed with

†Demoxepam is the U. S. adopted name for 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide.

‡Oxazepam, 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one, is the active ingredient in Serax; Wyeth, Inc., Radnor, Pa.

§This reaction was first carried out in our laboratories by Dr. G. Archer.

C_6H_6 and then petr ether to give 3.5 g (80%) of **7**, mp 254–256° dec. This reaction was repeated again on the same scale and the combined product, without further identification was treated with 85% $H_2NNH_2 \cdot H_2O$ (0.9 g, 0.015 mole) and a mixture of 810 ml of ethanol–890 ml of $CHCl_3$. After heating under reflux for 2 hr, the soln was acidified with 0.1 *N* HCl and heated under reflux for another 15 min. The soln was evapd and the residue boiled with 500 ml of EtOH and filtered to remove insoluble solid (discarded). The filtrate was heated under reflux overnight and concd to dryness, and the yellow residue was dissolved in EtOH and filtered over silica gel with EtOH as eluant. Evaporation gave 1.1 g of **8** which was recrystd from EtOH–C_6H_6, mp 274–276°, nmr (DMSO-d_6) δ 4.1 (s, 2H), 6.5, 7.0 (q, 2H, J_{AB} = 2.5 Hz). *Anal.* ($C_{15}H_{11}ClN_2O_2$) C, H, N.

7-Chloro-9-hydroxy-1,3-dihydro-5-phenyl-2*H*-benzodiazepin-2-one 4-Oxide (9). A soln of **8** (1 g, 0.0035 mole) in a mixture of 100 ml of CH_2Cl_2–50 ml of $CHCl_3$ was treated with *m*-chloroperbenzoic acid (0.8 g, 0.0046 mole) and stirred overnight at room temp. The ppt was filtered, washed with CH_2Cl_2–petr ether (1:1), and air-dried to yield 0.75 g (70% of **9**, mp 235–239° dec). Recrystn from C_6H_6–CH_3OH gave white needles, mp 236–238° dec. *Anal.* ($C_{15}H_{11}ClN_2O_3$) C, H, N.

5-Benzoyl-7-chloro-2*H*-1,4-benzoxazin-3(4*H*)-one (10). A suspension of **6** (2.5 g, 0.01 mole) in 25 ml of C_6H_6 was treated dropwise with bromoacetyl bromide (2.4 g, 0.012 mole) in 3 ml of C_6H_6 and then heated under reflux for 1.5 hr. After cooling to *ca.* 50°, the soln was decanted from a gummy residue and poured into a stirred mixture of 100 ml of CH_2Cl_2–100 ml of ice H_2O. After being made alk with $NaHCO_3$ (satd), the organic phase was separated, washed, dried, and concd. The gummy residue was dissolved in CH_2Cl_2–C_6H_6 (3:1) and filtered over Florisil to give after concn 2.6 g (70%) of the bromoacetamido deriv of **6** as off-white crystals, mp 145–147°. This solid was dissolved in 50 ml of CH_2Cl_2 and was added dropwise with stirring to 15 ml of liquid NH_3. After all the NH_3 had evapd, H_2O was added and the CH_2Cl_2 layer was separated, washed, dried, and concd to give 1.8 g of greenish yellow solid, mp 115–120°. After filtering over silica gel with the aid of EtOAc–hexane, **10** was obtained as yellow crystals, mp 128–130°. Recrystn from CH_2Cl_2–hexane gave yellow needles, mp 134–135°, ir ($CHCl_3$) ν_{max} 1700 cm^{-1} (C=O). *Anal.* ($C_{15}H_{10}ClNO_3$) C, H, N.

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Antifungal Activity of 7- and 5,7-Substituted 8-Quinolinols†

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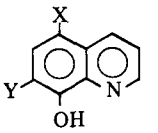
Although 8-quinolinol and some of its derivatives have been known to exhibit excellent antifungal properties, the mechanism of action of this class of compounds is not yet fully understood. A systematic approach has been undertaken to study 8-quinolinol and its derivatives with respect to structure-activity relationships and cell penetration of their copper(II) chelates.[1-4] As part of this study, it was of interest to examine the fungitoxicity of the 7-halo- and 5,7-dihalo-8-quinolinols in which the two substituents of the disubstituted derivatives were different. In addition to these compounds, four nitro-8-quinolinols were included to complete earlier reports,[3,4] as was also 5,7-difluoro-8-quinolinol.[2]

Of the compounds tested (Table II), the preparation of the following 8-quinolinols was previously reported: 7-fluoro,[5] 7-chloro,[6] 7-bromo,[6] 7-iodo,[6] 7-nitro,[7] 5-fluoro-7-iodo,[8] 7-bromo-5-chloro,[9] 5-chloro-7-iodo,[10] 5-bromo-7-chloro,[11] 5-bromo-7-iodo,[12] 5-bromo-7-nitro,[5] 7-chloro-5-iodo,[5] 7-bromo-5-iodo,[13] 5-iodo-7-nitro,[5] and 7-fluoro-5-nitro.[5]

Table I. 5,7-Disubstituted 8-Quinolinols



X	Y	Yield, %	Mp, °C[a]	Formula	Analyses
F	F	41	170–172[b]	$C_9H_5F_2NO$	C, H, F, N
F	Cl	61	172[c]	C_9H_5ClFNO	C, H, F, N
F	Br	91	172[d]	C_9H_5BrFNO	C, H, F, N
Cl	F	5.5	169–170[c]	C_9H_5ClFNO	C, H, F, N
Br	F	88	171–171.5[e]	C_9H_5BrFNO	C, H, Br, F, N
I	F	95	168–169[f]	C_9H_5FINO	C, H, F, I, N
Br	Cl	60	199–201[g]	$C_9H_5BrClNO$	C, H, N
I	Br	85	204 dec[h]	C_9H_5BrINO	C, H, N
Br	I	85	203 dec[i]	C_9H_5BrINO	C, H, N

[a] Analytical sample. [b] From cyclohexane–methylene chloride, *cf.* ref 16. [c] From EtOH. [d] From EtOH, *cf.* ref 17, where the compound was prepared but not characterized. [e] From cyclohexane–carbon tetrachloride. [f] From cyclohexane. [g] From MeOH, *cf.* ref 11, mp 189°. [h] From MeOH–DMF, *cf.* ref 13, mp 145–146°. [i] From MeOH–DMF, *cf.* ref 12.

All of the compounds were tested for purity by gas chromatographing their trimethylsilyl derivatives. It was found that a number of materials prepared by the methods of the literature were mixtures of products and not pure compounds. These had to be reinvestigated. 5-Iodo-7-chloro-8-quinolinol is typical of this group of compounds that was subsequently prepared correctly in an earlier work.[5] This was generally the case when it was desired to substitute a more electronegative halogen atom into the 7 position of a 5-halo-8-quinolinol which contained a less electronegative halogen substituent. The problem was overcome by starting with the halo-8-quinolinol which contained the more negative halogen atom in the desired position or by halogenating with the second halogen under controlled prototropic conditions.[14]

5,7-Difluoro-8-quinolinol was prepared by allowing 5-fluoro-8-quinolinol to react with trifluoromethyl hypofluorite. For the preparation of 7-chloro-5-fluoro-8-quinolinol, 5-fluoro-8-quinolinol was chlorinated by means of sulfuryl chloride in acetic acid, and 7-bromo-5-fluoro-8-quinolinol was also prepared from 5-fluoro-8-quinolinol by reaction with bromine in acetic acid. 5-Chloro-7-fluoro-8-quinolinol was prepared from 7-amino-5-chloro-8-quinolinol by a Baltz–Schiemann reaction, and 5-bromo- and 5-chloro-7-fluoro-8-quinolinols were obtained by halogenating 7-fluoro-8-quinolinol with the respective *N*-halosuccinimide in chloroform.

The data characterizing the new compounds are contained in Table I. All of the compounds were tested for antifungal activity according to published methods.[1] To Sabouraud

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