Photochemical Reaction of 14. Irradiation of a 1:1 mixture of **14** and **15** (100 mg, 0.33 mmol) in methylene chloride for 1 h gave **28** (45 mg, 90%) as yellow crystals: mp >300 °C (ethyl acetate); IR (Nujol) 1790, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) 1.55, 2.14 (AB q, J = 10.0 Hz, 2 H), 3.58 (br s, 4 H), 3.89 (br s, 2 H), 7.70, 8.10 (AA'BB', 4 H); mass spectrum, m/z 304 (M^+). Anal. ($C_{19}H_{12}O_4$) C, H.

The filtrate was shown to be mainly composed of **15** by ^1H NMR and IR spectra.

Transannular Cyclization of 22. Compound **22** (65 mg, 0.25 mmol) was dissolved in chloroform (1 mL) and exposed to atmospheric moisture for 3 days. The precipitated solids were collected by filtration and recrystallized from ethyl acetate to give **24** (66 mg, 95%) as colorless crystals: mp >300 °C; IR (Nujol) 3420, 1760 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.36, 1.68 (AB q, J = 9.2 Hz, 2 H), 3.24-3.60 (m, 6 H), 6.28 (s, 2 *H*), 8.41 (s, D_2O exchangeable, 2 H); UV (CH_3CN) 303 nm (ϵ 4500); mass spectrum, m/z 272 (M^+), 254 (M - 18). Anal. ($C_{15}H_{12}O_5$) C, H.

Acetylation of 24. To a solution of **24** (95 mg, 0.35 mmol) in pyridine (5 mL) were added acetic anhydride (5 mL) and a trace of 4-(dimethylamino)pyridine. The resulting solution was stirred at room temperature for 3 days and then diluted with water. The mixture was extracted with ethyl acetate, dried over anhydrous Na_2SO_4, evaporated under reduced pressure, and crystallized from ether to give **25** (60 mg, 48%) as colorless needles: mp 283-285 °C; IR (Nujol) 1778, 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54, 2.18 (AB q, J = 10.0 Hz, 2 H), 2.34 (s, 6 H), 3.44 (br s, 4 H), 3.62 (br s, 2 H), 7.05 (s, 2 H); mass spectrum, m/z 356 (M^+). Anal. ($C_{19}H_{16}O_7$) C, H.

Acknowledgment. We are indebted to Dr. Shiro Morita, who provided technical assistance during earlier stages of this work.

Registry No. **4**, 23077-93-2; **5**, 78456-63-0; **6**, 1709-63-3; **7**, 78456-64-1; **8**, 78456-65-2; **9**, 78456-66-3; **10**, 78456-67-4; **11**, 78512-50-2; **12**, 78456-68-5; **13**, 78512-51-3; **14**, 78456-69-6; **15**, 78512-52-4; **16**, 78513-24-3; **18**, 78456-70-9; **19**, 78512-53-5; **20**, 78456-71-0; **21**, 78514-61-1; **22**, 78456-72-1; **24**, 78456-73-2; **25**, 78456-74-3; **27**, 78456-75-4; **28**, 78456-76-5; naphthazarin, 475-38-7; cyclopentadiene, 542-92-7; quadricyclane, 278-06-8; anthracene, 120-12-7.

Supplementary Material Available: Table II, LUMO energies and coefficients (1 page). Ordering information is given on any current masthead page.

Potential Diuretic-β-Adrenergic Blocking Agents: Synthesis of 3-[2-[(1,1-Dimethylethyl)amino]-1-hydroxyethyl]-1,4-dioxino[2,3-*g*]quinolines

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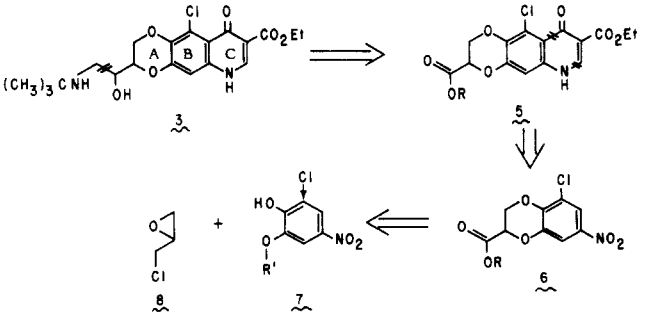
Received February 23, 1981

A series of hybrid structures were designed as potential diuretic-β-adrenergic blocking agents on the basis of the structures of the diuretic quincarbate (**2**) and a benzodioxane β blocker, **1**. Synthesis of the hybrids **50** and **51** as well as improved synthesis of the parent drugs **1** and **2** were developed. The key intermediate in the synthesis of **50** and **51** was the tricyclic diester **29** in which the quinolone functionality was masked as the corresponding 4-chloroquinoline. Discrimination between the methyl and ethyl esters in **29** was achieved by selective hydrolysis of the methyl ester and set the stage for attachment of the amino alcohol side chain and subsequent unmasking of the quinolone. Phosphoryl chloride induced cyclization of the adduct **25** afforded the tricyclic diester **29** along with the dioxino[2,3-*f*]quinoline **27** as the minor side product. The adduct **25** was prepared from the 2-(hydroxymethyl)-7-nitrobenzodioxane **15** which, in turn, was available from the monoprotected catechols **11** and **12**. Construction of the monoprotected catechols solved most of the regiochemical problems posed by the structures **50** and **51**. The tricyclic amino alcohols **50** and **51** were essentially devoid of diuretic and β-adrenergic blocking activity.

The most important first-line drug therapies for essential hypertension are diuretics[2] and β-adrenergic blocking agents.[3] In many instances, neither of these drugs alone adequately controls blood pressure, and, as a result, combinations of β blockers and diuretics have been subjected to extensive clinical trials with encouraging results.[4] An attractive alternative to this combination therapy would be a single entity exhibiting both of the desired pharmacological actions. The tricyclic amino alcohols **3** and **4** were designed as potential β-blocker diuretics after considering the structures of the known β blocker **1**[5] and the diuretic

Scheme I



(1) Present address: Biomedical Research Department, ICI Americas Inc., Wilmington, DE 19897.

(2) Dirks, J. H. "Hospital Practice"; New York: H. P. Publishing Co., 1979; pp 99-110.

(3) Heikkilä, J.; Jounela, A.; Katila, M.; Luomanmäki, K.; Frick, M. H. *Ann. Clin. Res.* **1979**, *11*, 267-89.

(4) (a) Castenfors, H. *Eur. J. Clin. Pharmacol.* **1977**, *12*, 97-103. (b) Neuvonen, P. J.; Pentikainen, P. J.; Jounela, A. J. *Br. J. Clin. Pharmacol.* **1978**, *6*, 363-7. (c) Bloem, T. J. J. M.; Disch, R. P.; Lindner, P. C. J. M.; Kerkhof, J. V. D. *Curr. Ther. Res.* **1978**, *24*, 26-30.

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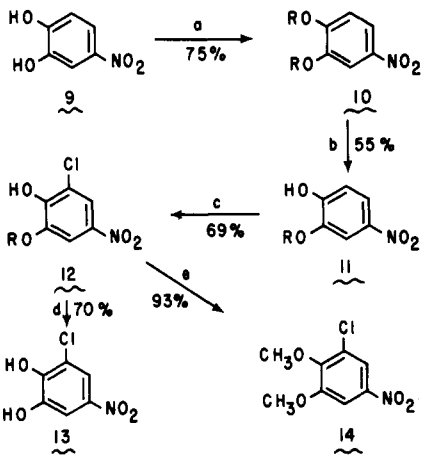
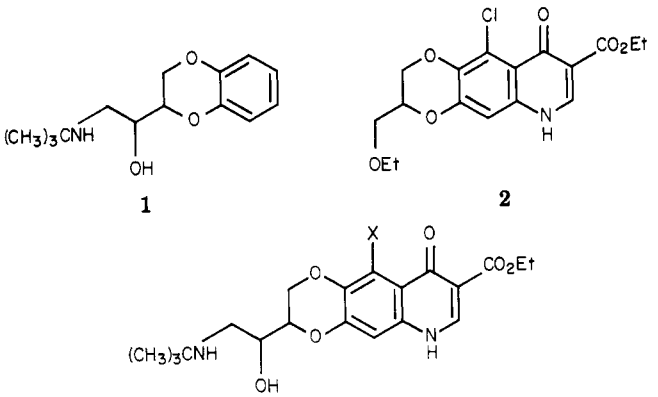
Scheme II[a,b]



[a] Series a, R = CH_3; series b, R = $PhCH_2$. [b] (a) RX, NaH, DMF; (b) KOH, H_2O, $CH_3OCH_2CH_2OH$; reflux; (c) Cl_2, HOAc; (d) 40% aqueous HBr, HOAc, reflux; (e) CH_3I, K_2CO_3, DMF, 60 °C.

quincarbate (2).[6] The syntheses of these hybrids are described herein.

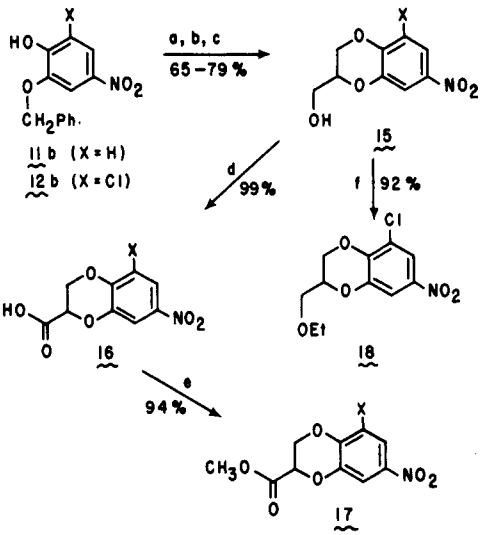


1 2

3, X = Cl
4, X = H

In the retrosynthetic analysis (Scheme I), attachment of the amino alcohol side chain late in the synthesis serves to postpone the attendant isomer separation and, therefore, was deemed desirable. Several methods are known for the stepwise construction of the amino alcohol side chain;[7] each method requires either the acid or aldehyde oxidation state at the point of formation of the final carbon–carbon bond. Thus, the tricyclic diester **5** becomes the key synthetic intermediate. In view of the various methods available for differentiation of methyl and ethyl esters,[8] the simplest choice for R in structure **5** was the methyl radical. Quinolone rings such as that incorporated in **5** can be constructed by known methods[9] from anilines, and precedent[9] suggested that the desired regiochemistry might be obtained. This disconnection leads to the substituted benzodioxane **6**. Regiochemical requirements for constructin

Scheme III[a,b]



[a] Series a, X = H; series b, X = Cl. [b] (a) epichlorohydrin, piperidine, reflux; (b) HCl, H_2O, HOAc, reflux; (c) KOH, H_2O; (d) Jones reagent, acetone, 15 °C; (e) CH_3I, $KHCO_3$, DMF; (f) EtI, NaH, HMPA, 20 °C.

of benzodioxane **6** suggest the monoprotected catechol **7** as a precursor.[10,11] Catechol **7** would also allow the requisite chlorine atom to be introduced with regiochemical control.

Preparation of the Aromatic Nucleus. The chemistry required for preparation of the desired monoprotected nitrocatechols was reported by Page and Clinton,[12] who demonstrated the selective cleavage of dialkyl ethers of nitrocatechols by hydroxide as well as halogenation of the resulting phenols. Thus, by use of their procedure, both the dimethyl ether **10a** and the dibenzyl ether **10b** could be selectively cleaved by base to give the monoprotected catechols **11** (Scheme II). Subsequent chlorination provided tetrasubstituted aromatic compounds **12** in which most of the regiochemical requirements had been satisfied. Cleavage of the methyl ether **12a** provided the disubstituted catechol **13** and alkylation gave the dimethyl ether **14**. These intermediates were important for aspects of this work which will be discussed elsewhere.

Construction of the Benzodioxane. Scheme III depicts construction of the benzodioxane ring from the monobenzyl ether **12b**. The monobenzyl ether **12b** was alkylated with epichlorohydrin in the presence of piperidine, the benzyl ether was then cleaved by acid,[11b] and finally, ring closure was effected with base to afford the benzodioxane **15b** in 65% overall yield. The success of this three-step process (without purification of intermediates) was predicated on complete removal of epichlorohydrin and dichlorohydroxypropane by addition and evaporation of xylene in the first step and similar removal of HCl and acetic acid by use of ethanol in the second step.

Attempts to obtain the benzodioxane **15b** from the more readily accessible monomethyl ether **12a** were thwarted when the intermediate alkylated product **19** could not be selectively deprotected. A variety of methods, including molten pyridinium hydrochloride, 40% aqueous HBr or concentrated HCl in acetic acid, and trimethylsilyl iodide[13]

(6) (a) van Dijk, J.; Hartog, J.; Boschman, T. A. C. *J. Med. Chem.* **1976**, *19*, 982. (b) Boschman, T. A. C.; Korsloot, J. G. U.S. Patent 3 865 832, 1975. (c) Boschman, T. A. C.; van Dijk, J.; Hartog, J.; Walop, J. N. In "Diuretic Agents"; Cragoe, E. J., Jr., Ed.; American Chemical Society: Washington, DC, 1978; p 140.

(7) See, for example: Chodnekar, M. S.; Crowther, A. F.; Hepworth, W.; Howe, R.; McLoughlin, B. J.; Mitchell, A.; Rao, B. S.; Slatcher, R. P.; Smith, L. H.; Stevens, M. A. *J. Med. Chem.* **1972**, *15*, 49 and references cited therein.

(8) McMurry, J. E. *Org. React.* **1976**, *24*, 187.

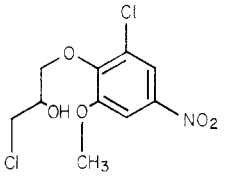
(9) (a) Gould, R. G., Jr.; Jacobs, W. A. *J. Am. Chem. Soc.* **1939**, *61* 2890. (b) Riegel, B.; Lappin, G. R.; Adelson, B. H.; Jackson, R. I.; Albisetti, C. J., Jr.; Dodson, R. M.; Baker, R. H. *Ibid.* **1946**, *68*, 1264.

(10) Stephenson, O. *J. Chem. Soc.* **1954**, 1571.

(11) (a) Augstein, J.; Green, S. M.; Monro, A. M.; Potter, G. W. H.; Worthing, C. R.; Wrigley, T. I. *J. Med. Chem.* **1965**, *8*, 446. (b) Paulsen, A. *Acta Polytech. Scand., Chem. Incl. Metall. Ser.* **1960**, *No. 6*, 11.

(12) Page, D. F.; Clinton, R. O. *J. Org. Chem.* **1962**, *27*, 218.

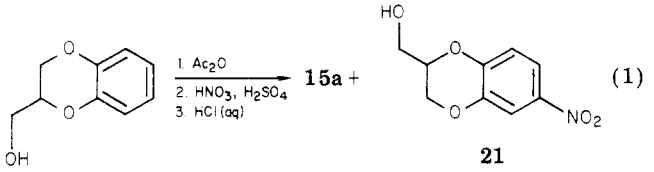
(13) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.



19

in carbon tetrachloride resulted in competitive cleavage of both the three-carbon ether and the methyl ether.

Direct nitration of the acetate of 2-(hydroxymethyl)-benzodioxane (**20**) was reported[11a,14] to give exclusively the desired 7-nitro derivative 15a. In fact, ^{13}C NMR spectra of the isolated reaction products readily verified that nearly equal amounts of the two isomers **15a** and **21** had formed (eq 1). With considerable effort **15a** could be induced to



(1)

20 21

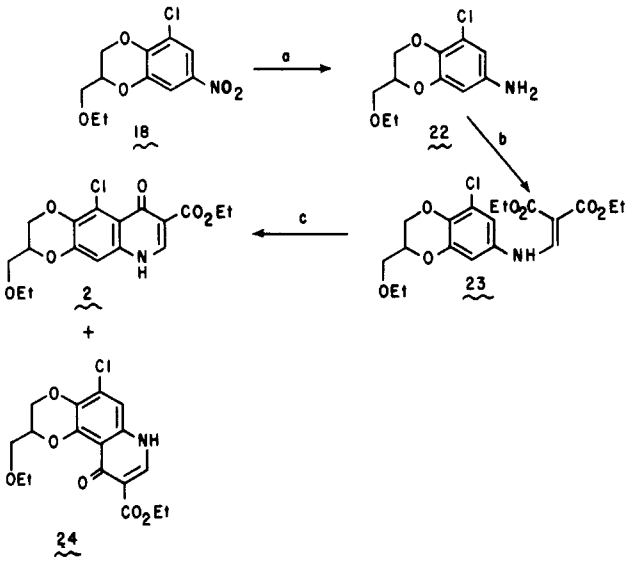
selectively crystallize. The fact that a very simple fractional crystallization of the desired isomer at a later stage in the synthesis was possible made this a practical route for the dechloro series **a**, leading to the tricyclic target **4** (see below).

Jones oxidation[15] of alcohols **15** provided nearly quantitative yields of the acids **16**. In order to simplify intermediate steps in their synthesis, we decided to protect the acids as their methyl esters **17**. Finally, the 2-ethoxymethyl derivative **18**, required for the synthesis of quincarbate (**2**) (Scheme IV), was readily available from the 2-(hydroxymethyl)benzodioxane **15b** by alkylation.

Construction of the Quinoline Ring. The most common quinolone synthesis[9] is demonstrated by the conversion of the nitrobenzodioxane **18** into quincarbate (**2**) as outlined in Scheme IV. This synthesis of quincarbate has been briefly outlined by van Dijk, Hartog, and Boschman,[6a] and the details have appeared in the patent literature.[6b] The conversion, as carried out in these laboratories, involved thermal cyclization of adduct **23** to give a 70:30 mixture of regioisomers **2** and **24**. The predominant, desired isomer **2** could be isolated by fractional crystallization from DMF to complete the synthesis of quincarbate.

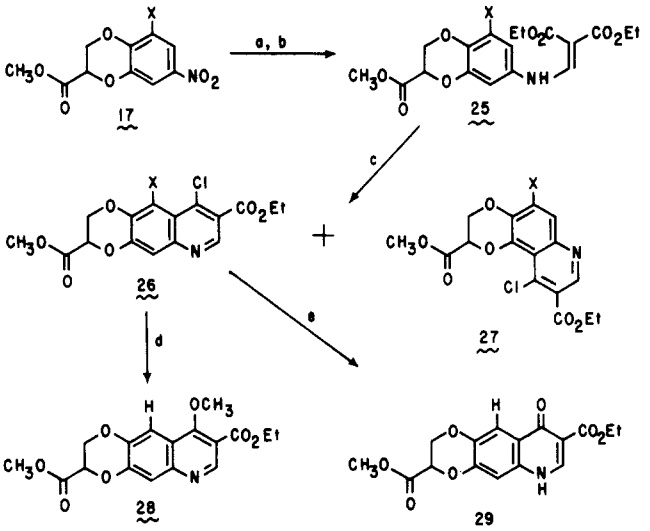
With ester functionality attached to the benzodioxane ring, as in the adduct **25**, thermal cyclization to form the quinolone ring is no longer successful. An alternative cyclization was reported by Agui, Mitani, Nakashita, and Nakagome,[16] who found that diethyl malonates such as **25** (Scheme V) could be induced to cyclize in refluxing phosphoryl chloride to provide 4-chloroquinolines directly. Synthesis of the key tricyclic intermediate **26** began with preparation of the adduct **25** in two steps from the nitrobenzodioxane **17**. When the sequence was carried out with a mixture of benzodioxanes **15a** and **21**, the desired isomer **25a** was isolated cleanly following a single recrystallization of the mixture from 2-propanol.

Scheme IV[a]



[a] (a) H_2, PtO_2, 50 psi; (b) $EtOCH{=}C(CO_2Et)_2$, 80 °C, −EtOH; (c) 200 °C, Dowtherm A.

Scheme V[a,b]



[a] Series a, X = H; series b, X = Cl. [b] (a) H_2, PtO_2, 50 psi; (b) $EtOCH{=}C(CO_2Et)_2$, 80 °C, −EtOH; (c) $POCl_3$, reflux; (d) CH_3OH, HCl; (e) HCl, aqueous Me_2SO.

Heating adducts **25** in refluxing phosphoryl chloride for a few hours[16] gave a mixture of tricyclic chloroquinolines **26** and **27**, with the desired linear isomer **26** predominating. The ratio of the two isomers (**26**/**27**) was 70:30 in the **a** series (X = H) and 80:20 in the **b** series (X = Cl). The improved solubility and chromatographic properties of these chloroquinolines compared to the corresponding quinolones (e.g., **29**) facilitated their separation by column chromatography.

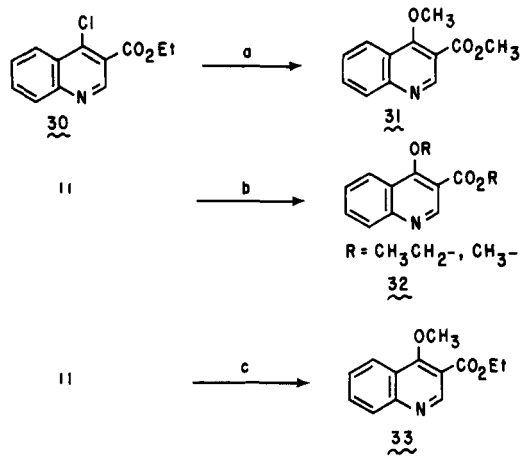
Masking of the quinolone as the more stable methoxy derivative **28** was briefly investigated as described in Scheme VI. Treatment of chloroquinoline **30** with sodium methoxide rapidly afforded the methyl ether methyl ester **31**. In an attempt to thwart the observed undesired transesterification, a mixture of chloroquinoline **30** and 1 equiv of methanol in THF was cooled to −78 °C and treated with 1 equiv of potassium *tert*-butoxide. Within a few minutes the chloroquinoline **30** was consumed, giving a mixture of ethers **32** in which ethyl and methyl radicals were evenly distributed between the ester and ether

(14) Marini-Bettòlo, G. B.; Vittory, R. L. *Gazz. Chim. Ital.* **1957**, *87*, 1038.

(15) (a) Djerassi, C.; Engle, R. R.; Bowers, A. *J. Org. Chem.* **1956**, *21*, 1547. (b) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, *39*.

(16) Agui, H.; Mitani, T.; Nakashita, M.; Nakagome, T. *J. Heterocycl. Chem.* **1971**, *8*, 357.

Scheme VI[a]



[a] (a) 1 equiv of $NaOCH_3$, CH_3OH; (b) 1 equiv of CH_3OH, THF, 1 equiv of $KOC(CH_3)_3$, −78 °C; (c) CH_3OH, HCl (catalyst).

functional groups. This result suggested that, under basic conditions, fast transesterification was preventing the clean conversion of the chloroquinoline **30** into the desired methyl ether ethyl ester **33**.

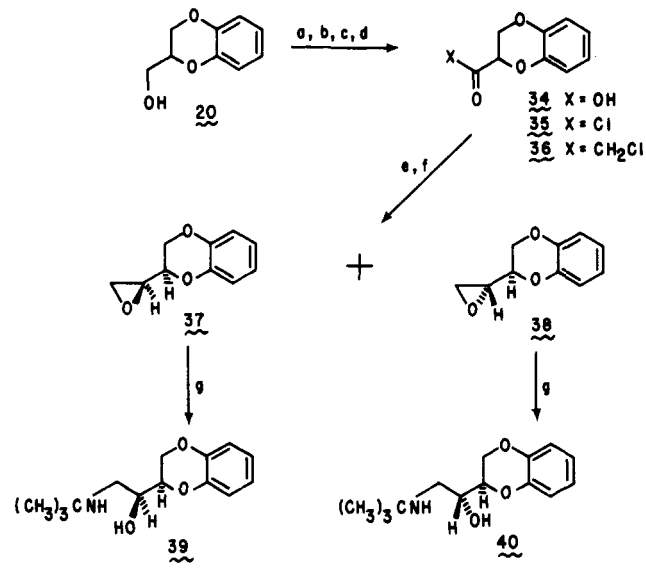
Finally, a selective method was discovered for introducing the methyl ether while leaving the ethyl ester intact. Treatment of chloroquinoline **30** with a trace of HCl (generated in situ by addition of 1 drop of acetyl chloride) in anhydrous methanol caused a slow but clean conversion to the methyl ether **33** with no sign of concomitant transesterification. These same conditions permitted the conversion of the more complex chloroquinoline **26a** into the methyl ether **28** in 79% yield. Subsequent studies showed that the methyl ethers, at least in the **a** series (X = H), were too unreactive. Hence, the chloroquinolines such as **26** were a more useful masked form of the quinolone.

Unmasking of the quinolones by hydrolysis of the chloroquinolines would ultimately be necessary. A serendipitous observation[17] suggested the most convenient and selective reaction conditions for achieving this conversion. Chloroquinoline **26** is converted cleanly to the quinolone **29** by treatment with aqueous HCl in dimethyl sulfoxide. Other solvents are much less satisfactory for this conversion.

Addition of the Amino Alcohol Side Chain. Syntheses of the amino alcohols **39** and **40** (Scheme VII) were reported earlier by Howe, Rao, and Chodnekar.[5] We also prepared these compounds by a somewhat different route in anticipation of the chemistry which would be necessary for the synthesis of the target hybrids.

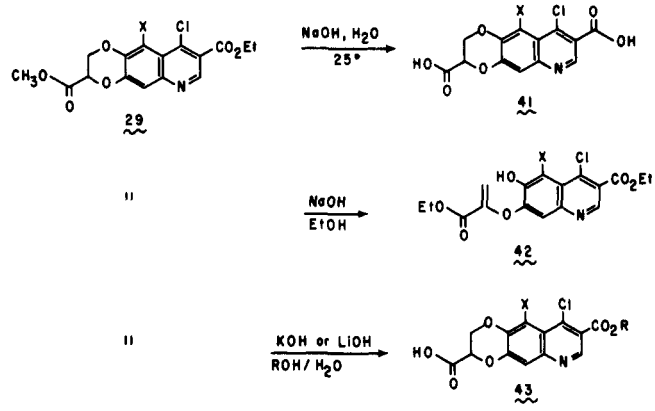
The three-step conversion of 2-(hydroxymethyl)benzodioxane (**20**) to the chloro ketone **36** took advantage of proven chemistry.[18,19] Reduction of the chloro ketone **36** with sodium borohydride followed by brief treatment with sodium hydroxide provided a mixture of the epoxides **37** and **38** which were separated by chromatography on silica gel. Each of the epoxides was converted to the corresponding amino alcohol **39** or **40** by treatment with excess *tert*-butylamine. Assignment of the relative configurations

Scheme VII[a]



[a] (a) $KMnO_4$, KOH, H_2O; (b) $SOCl_2$, benzene 25 °C; (c) CH_2N_2, ether; (d) anhydrous HCl, ether; (e) $NaBH_4$, CH_3OH; (f) NaOH, CH_3OH; (g) *t*-$BuNH_2$, EtOH, reflux.

Scheme VIII[a]



[a] Series a, X = H; series b, X = Cl.

of the amino alcohols **39** and **40** (and thereby the epoxides **37** and **38**) is based on the NMR arguments of Howe, Rao, and Chodnekar.[5] We have confirmed this assignment by determination of the single-crystal structure of amino alcohol **40** by X-ray diffraction.[20]

A prerequisite for applying this chemistry to the tricyclic series was selective cleavage of the methyl ester in the diesters **29** (Scheme VIII). Solubility factors led to an equal mixture of recovered starting material and the diacid **41a** when the hydrolysis of diester **29a** was attempted with 1 equiv of sodium hydroxide in water. Although replacement of water in the reaction mixture with ethanol eliminated the formation of diacid **41a**, cleavage of the benzodioxane ring became competitive with ester hydrolysis.[21] The diethyl ester **42a** was tentatively identified as the

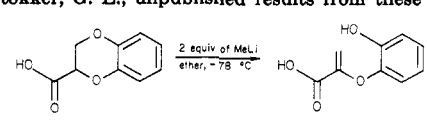
(17) During a ^{13}C NMR study of tautomerism of the quinolone ring system, Dr. D. W. Cochran of these laboratories noted the rapid destruction of chloroquinoline **26b** in wet Me_2SO-d_6. Closer examination indicated that this destruction was simply clean hydrolysis to the corresponding quinolone.

(18) Rosnati, V.; de Marchi, F. *Gazz. Chim. Ital.* **1961**, *91*, 605.

(19) Koo, J.; Avakian, S.; Martin, G. J. *J. Am. Chem. Soc.* **1955**, *77*, 5373.

(20) Springer, J. P.; Hirshfield, J. M., Merck Sharp and Dohme Research Laboratories, unpublished results.

(21) A similar cleavage of a benzodioxane ring was also noted in attempts to convert the carboxylic acid i to the corresponding methyl ketone: Stokker, G. E., unpublished results from these laboratories.



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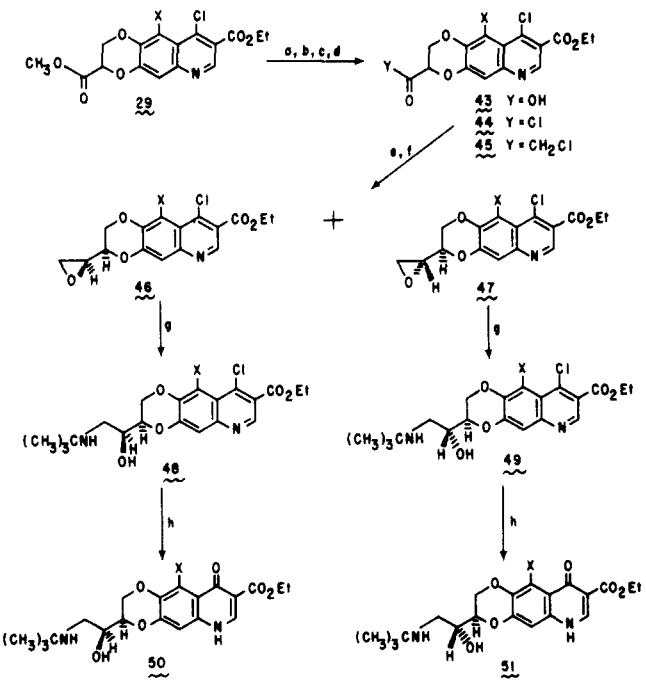
Scheme IX[a,b]



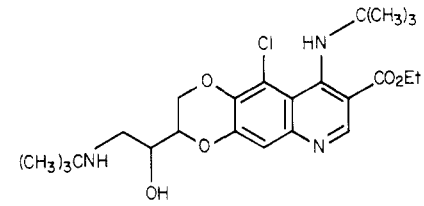
[a] Series a, X = H; series b, X = Cl. [b] (a) For X = H the reagents were KOH, EtOH, and H_2O, and for X = Cl the reagents were LiOH, EtOH, and H_2O; (b) $(COCl)_2$, 0 °C; (c) CH_2N_2, ether, THF; (d) HCl, ether, THF; (e) $NaBH_4$, EtOH, 0 °C; (f) NaOH, THF, EtOH; (g) for X = H the conditions were $(CH_3)_3CNH_2$, EtOH, reflux, and 2 h, and for X = Cl the conditions were $(CH_3)_3CNH_2$, CF_3CH_2OH, 20 °C, and 72 h; (h) aqueous HCl, Me_2SO.

product of this process. Successful hydrolysis required careful selection of the water–ethanol solvent ratio in order to balance solubility problems and diacid formation with ring cleavage. In ethanol–water (9:1) a 91% yield of acid **43a** was obtained with no concomitant ring cleavage. Benzodioxane cleavage could not be completely suppressed during the hydrolysis of diester **29b**, and, in this case, the ethyl ester **42b** was isolated. If methanol was substituted for ethanol in the hydrolysis, up to 30% transesterification of the ethyl ester was observed.

With the acids **43** in hand, further construction (Scheme IX) of the amino alcohol side chain followed the route described previously (Scheme VII) for benzodioxanes **39** and **40**. No recognizable acid chloride resulted from treatment of acids **43** with thionyl chloride. Oxalyl chloride, on the other hand, rapidly and cleanly converted the acids to the corresponding acid chlorides **44**. Sequential treatment of the acid chlorides **44** with diazomethane and HCl under strictly anhydrous conditions provided the chloro ketones **45**. Reduction with sodium borohydride and cyclization of the resulting chlorohydrins gave, in each case, a mixture of epoxides **46** and **47**.

The first instance in the entire synthesis where the presence of the 10-chloro substituent significantly affected reactivity was the reaction of the epoxides **46** and **47** with *tert*-butylamine. The mixture of epoxides **46a** and **47a** was treated with 2 equiv of *tert*-butylamine in ethanol at reflux for 2 h to give the amino alcohols **48a** and **49a**. These diastereoisomers were separated by chromatography. Isomer separation was accomplished at the epoxide stage for epoxides **46b** and **47b**, again by chromatography. Treatment of these epoxides as described above gave the diadduct **52** as the major product.

Reaction of *tert*-butylamine with epoxides **46b** and **47b** in aprotic solvents was very slow. Both water and $LiClO_4$



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catalyzed the reaction in THF but did not improve the selectivity. We considered that enhancement of the hydrogen bond donating properties of the solvent might favor reaction at the epoxide center. When trifluoroethanol was substituted for ethanol and the reaction was carried out as above (reflux), formation of the side product **52** was diminished. The best conditions found for selective epoxide opening were treatment of **46b** or **47b** with 5 equiv of *tert*-butylamine in trifluoroethanol at room temperature. Complete consumption of the epoxide required 72 h and was accompanied by formation of about 15% of the diadduct **52**.

Unmasking of the quinolone rings completed the syntheses of the hybrids **50** and **51**. We took advantage of the observation mentioned above that acid-catalyzed hydrolysis was extremely facile in Me_2SO.[17] Again the enhanced reactivity of the quinoline nucleus bearing the 10-chlorine was noted. Hydrolysis of the chloroquinolines **48a** and **49a** with aqueous HCl in Me_2SO required 3 h, whereas, hydrolysis of the dichloro derivatives **48b** and **49b** was complete within 15 min under the same conditions.

All four of the final targets were essentially devoid of diuretic and β-adrenergic blocking activity. The syntheses of these products, however, required development of new procedures for construction of this family of heterocycles. Masking of 1,4-dihydro-4-oxoquinolines as the corresponding 4-chloroquinolines and 4-methoxyquinolines was fully exploited. Selective conditions for several reactions were developed which should be useful in other synthetic endeavors.

Experimental Section

General Methods. Complete experimental details for each reaction depicted in the schemes are provided as supplementary material. Selected experimental procedures are presented here.

All reactions which were potentially sensitive to atmospheric moisture or oxygen were run in an atmosphere of purified nitrogen. "Dry" solvents were dried as follows: "reagent grade" dimethylformamide (DMF) and hexamethylphosphoramide (HMPA) were dried over 4A molecular sieves; tetrahydrofuran (THF) was distilled from a blue solution of benzophenone ketyl; diethyl ether (anhydrous ether) was obtained from Mallinckrodt and was used from a freshly opened can.

Diethyl [[[2-(Methoxycarbonyl)-5-chloro-1,4-benzodioxan-7-yl]amino]methylene]malonate (25b). A solution of 8.87 g (32.49 mmol) of the nitro ester **17b** in 200 mL of absolute ethanol was hydrogenated on a Parr apparatus at 50 psi of H_2 in the presence of 500 mg of PtO_2. The calculated amount of hydrogen was taken up in 1 h. The solution was vacuum filtered to remove the catalyst, and the ethanol was evaporated. To the residue was added 7.02 g (32.49 mmol) of diethyl (ethoxymethylene)malonate, and the resulting mixture was heated for 1 h on a steam bath under water-aspirator vacuum to give a homogeneous liquid. This liquid was dissolved in hot 2-propanol (120 mL) and allowed to crystallize. This gave 10.15 g (75%) of fine white needles, mp 130–131.5 °C. An analytical sample was prepared by recrystallization from 2-propanol to give fine white needles: mp 130–131.5 °C; NMR ($CDCl_3$) δ 1.31 and 1.36 (t, 3 H, J = 7 Hz, CH_2CH_3), 3.84 (s, 3, CH_3O), 4.27 and 4.33 (q, 2, J = 7 Hz, CH_2CH_3), 4.50 (m, 2, $OCHCH_2O$), 4.92 (t, 1, J = 3.5 Hz, CH), 6.81 (s, 2, aromatic H), 8.39 (d, 1, J = 14 Hz, vinylic H), 10.9 (br d, 1, J = 14 Hz, CH), 6.81 (s, 2, aromatic H), 8.39 (d, 1, J = 14 Hz, vinylic H), 10.9 (br d, 1, J = 14 Hz, NH); IR ($CHCl_3$) 1768,

1705, 1695, 1660, 1615, 1585, 1500, 1255, 1150 cm^{-1}.

Anal. Calcd for $C_{18}H_{20}ClNO_6$: C, 52.24; H, 4.87; N, 3.38. Found: C, 52.25; H, 5.09; N, 3.36.

Ethyl 9,10-Dichloro-2,3-dihydro-3-(methoxycarbonyl)-1,4-dioxino[2,3-*g*]quinoline-8-carboxylate (26b) and Ethyl 5,10-Dichloro-2,3-dihydro-2-(methoxycarbonyl)-1,4-dioxino-[2,3-*f*]quinoline-9-carboxylate (27b). A solution of 3.0 g (7.25 mmol) of the (aminomethylene)malonate **25b** in 20 mL of phosphoryl chloride was stirred at reflux for 18 h. Evaporation of the phosphoryl chloride was followed by addition and similar removal of two portions of xylene. The resulting red wax was dissolved in dichloromethane and shaken with ice-cold 5% aqueous NaOH solution. After dilution with ether, the organic phase was isolated, washed with water and saturated brine, and dried ($MgSO_4$). Evaporation of the solvents left 2.7 g of an orange solid. NMR analysis indicated that this was an 80:20 mixture of the two cyclization products **26b** and **27b**. The two isomers were separated by flash chromatography[22] on silica gel with 10% ether/dichloromethane as eluant. A portion of the more mobile, minor isomer **27b** was recrystallized from hexane to give yellow needles: mp 137–138.5 °C; NMR ($CDCl_3$) δ 1.42 (t, 3, J = 7 Hz, CH_3CH_2), 3.84 (s, 3, CH_3O), 4.47 (q, 2, J = 7 Hz, CH_3CH_2O), 4.6 (m, 2, C_3H's), 5.10 (t, 1, J = 3 Hz, C_2H), 7.87 (s, 1, C_6H), 8.90 (br, s, 1, C_8H); IR ($CHCl_3$) 1768 (m), 1735 (s), 1605 (m), 1585 (m), 1550 (s), 1485 (s), 1423 (s), 1330 (s), 1272 (s), 1106 (s) cm^{-1}; UV max (ethanol) 216 nm (log ε 4.27) 262 (4.82), 309 (3.50), 355 (3.43).

Anal. Calcd for $C_{16}H_{13}Cl_2NO_6$: C, 49.76; H, 3.39; N, 3.62. Found: C, 49.96; H, 3.35; N, 3.53.

A portion of the less mobile, major isomer **26b** was recrystallized from hexane–dichloromethane to provide fine white needles: mp 174–175 °C; NMR ($CDCl_3$) δ 1.44 (t, 3, J = 7 Hz, CH_3CH_2O), 3.87 (s, 3, CH_3O), 4.51 (q, 2, J = 7 Hz CH_3CH_2O), 4.65 (m, 2, C_2H's), 5.07 (t, 1, J = 3 Hz, C_3H), 7.75 (s, 1, C_5H), 8.92 (s, 1, C_7H); IR ($CHCl_3$) 1766 (m), 1732 (s), 1538 (m), 1585 (m), 1488 (s), 1450 (s), 1320 (s), 1159 (s), cm^{-1}; UV max (ethanol) 223 nm (log ε 4.33), 259 (4.70), 331 (3.89), 343 (3.90).

Anal. Calcd for $C_{16}H_{13}Cl_2NO_6$: C, 49.76; H, 3.39; N, 3.62. Found: C, 49.71; H, 3.41; N, 3.46.

9-Chloro-8-(ethoxycarbonyl)-2,3-dihydro-1,4-dioxino[2,3-*g*]quinoline-3-carboxylic Acid (43a). A suspension of 620 mg (1.76 mmol) of the diester **29a** in 14.0 mL of 0.139 M KOH in ethanol–water (9:1; 1.94 mmol, 1.1 equiv) was stirred at 0 °C for 30 min. The homogeneous reaction mixture was then diluted with water (130 mL) and acidified by addition of acetic acid (2 mL). The precipitate was collected by filtration and dried to give 543 mg (91%) of the desired monocarboxylic acid **43a** as a white solid: NMR (CF_3CO_2D) δ 1.53 (t, 3, J = 7 Hz, CH_3), 4.70 (q, 2, J = 7 Hz, CH_2CH_3), 4.8 (m, 2, $CHCH_2O$), 5.38 (t, 1, J = 3 Hz, $CHCH_2O$), 7.87 and 8.20 (s, 1, aromatic H), 9.30 (s, 1, CH=N); IR (KBr) 3200–2700 (br, CO_2H,OH), 1695 (C=O), 1710 (sh), 1475 (s).

Anal. Calcd for $C_{15}H_{12}ClNO_6$: Cl, 10.50. Found: Cl, 10.64.

A second hydrolysis under similar conditions but with *methanol*–water (9:1) as the solvent resulted in a comparable yield of the monocarboxylic acid **43a**. However, NMR analysis indicated that approximately 60% of the ethyl ester had been converted under these conditions to the correspnding methyl ester: NMR (CF_3CO_2D) δ 4.21, s, CH_3O). The diester **29a** shows a different chemical shift for the methyl ester at carbon 3: NMR (CF_3CO_2D) δ 3.98 (s, CH_3O).

A third hydrolysis was attempted with 2.0 equiv of NaOH in water (0.1 N). After 4 h at room temperature the suspension initially present had dissolved. Acidification of small aliquots (pH 2 or 4) caused no precipitation. The reaction mixture was evaporated and dried at 25 °C (0.1 mm). The residue dissolved completely in CF_3CO_2D and was identified as the diacid **41a**: NMR (CF_3CO_2D) δ 4.77 (m, 2, OCH_2CHO), 5.37 (t, 1, J = 3 Hz, CH_2CHO) 7.83 and 8.23 (s, 1, aromatic H), 9.35 (s, 1, CH=N). Hydrolysis with 1 equiv of NaOH in water (0.1 N) after 4 h gave a mixture of diacid **41a** and starting diester **29a**.

Hydrolyses were also performed with NaOH (1.0 equiv) in ethanol–THF–water (11:3:1) and with KOH (1.0 equiv) in methanol. The reaction mixture turned yellow in each case. Dilution with water and acidification with acetic acid as described above provided a precipitate which was collected and dried. NMR analysis indicated that, in each case, the product consisted of a mixture of the desired ester **43a** (including some transesterification in the KOH/methanol product) along with about 50% of a new product resulting from cleavage of the benzodioxane ring which was tentatively assigned the structure **42a**: NMR (CF_3CO_2D) δ 6.07 and 6.63 (d, 1, J = 3 Hz, $=CH_2$).

9,10-Dichloro-8-(ethoxycarbonyl)-2,3-dihydro-1,4-dioxino[2,3-*g*]quinoline-3-carboxylic Acid (43b). A suspension of 2.0 g (5.18 mmol) of the diester **29b** in 100 mL of ethanol–water (9:1) was stirred at 0 °C while 2.85 mL (5.70 mmol) of 2.0 N LiOH in water was added dropwise over 10 min. Following the addition, the reaction mixture was stirred at 0 °C for 1 h. After addition of 8.0 mL of acetic acid, the reaction mixture was filtered to remove a small amount of insoluble material. The filtrate was evaporated at 50 °C, and water (100 mL) was added. The precipitate was collected by filtration and dried in a stream of air to give 1.84 g of a white solid. This material was suspended in ether–hexane (1:1, 100 mL). The suspension was stirred for 15 min and then filtered. The precipitate, after drying in air, amounted to 1.56 g (81%) of the desired monocarboxylic acid **43b**: NMR (CF_3CO_2D) δ 1.57 (t, 3, J = 7 Hz, CH_3), 4.67 (q, 2, J = 7 Hz, CH_2CH_3), 4.9 (m, 2, OCH_2CHO), 5.38 (t, 1, J = 3 Hz, CHO), 7.83 (s, 1, aromatic H), 9.13 (s, 1, CH=N); IR (KBr) 3100–2700 (OH and CO_2H), 1735 (C=O), 1620 (w) 1580 (w), 1553 (w), 1485 (s), 1445 (s) cm^{-1}.

Ethyl 4,5-Dichloro-7-[[1-(ethoxycarbonyl)ethenyl]oxy]-6-hydroxyquinoline-3-carboxylate (42b). The ether/hexane wash from the preparation of acid **43b** above was evaporated. The major component of the resulting mixture was isolated by flash chromatography[22] on silica gel with 10% ether–dichloromethane. Further purification by recrystallization from butyl chloride gave the diester **42b** as light yellow needles: mp 135–136 °C; NMR ($CDCl_3$) δ 1.26 and 1.43 (t, 3, J = 7 Hz, CH_3), 4.26 and 4.48 (q, 2, J = Hz, CH_2CH_3), 5.63 and 6.20 (d, 1, J = 2 Hz, $C=CH_2$), 7.57 (s, 1, aromatic H), 8.87 (s, 1, CH=N); IR ($CHCl_3$) 3700 and 3520 (OH), 3010–2975 (CH), 1730 (C=O), 1645 (w), 1580 (w), 1550 (w), 1490 (s), 1455 (s) cm^{-1}.

Anal. Calcd for $C_{17}H_{15}Cl_2NO_6$: C, 51.02; H, 3.78; N, 3.50. Found: C, 51.24; H, 3.72; N, 3.54.

Ethyl 9,10-Dichloro-3-(chlorocarbonyl)-2,3-dihydro-1,4-dioxino[2,3-*g*]quinoline-8-carboxylate (44b). The acid **43b** (10 g, 2.69 mmol) was added over 5 min to 25 mL of stirred oxalyl chloride (freshly distilled) at 0 °C. Following the addition, the resulting suspension was stirred for an additional 30 min at 0 °C. Excess oxalyl chloride was evaporated, and the residual solid was dried at 25 °C (0.1 mm) to give the acid chloride **44b** as a light yellow solid: NMR ($CDCl_3$) δ 1.45 (t, 3, J = 7 Hz, CH_3), 4.55 (q, 2, J = 7 Hz, CH_2CH_3), 4.71 (dd, 1, J = 3, 12 Hz, OCH_2CHO), 5.22 (dd, 1, J = 2, 12 Hz, OCH_2CHO), 5.65 (m, 1, OCH_2CHO), 8.62 (s, 1, aromatic H), 9.18 (s, 1, CH=N).

Ethyl 9,10-Dichloro-3-(2-chloro-1-oxoethyl)-2,3-dihydro-1,4-dioxino[2,3-*g*]quinoline-8-carboxylate (45b). A solution of 60 mmol of diazomethane[27] in 300 mL of dry ether–THF (2:1) was stirred at 0 °C under a nitrogen atmosphere. To this stirred solution was added a suspension of 7.73 g (19.8 mmol) of the acid chloride **44b** in 100 mL of THF over 15 min. Stirring was continued for 1.25 h at 0 °C to effect complete conversion to diazo ketone [IR (neat) 2100 cm^{-1}]. The suspension was warmed to 20 °C, and gaseous HCl was bubbled into the suspension for 1 h, after which no diazo ketone remained (IR). The reaction mixture was slowly poured into a rapidly stirred mixture of aqueous Na_2CO_3 and dichloromethane at 0 °C. Extraction with dichloromethane gave 4.97 g (62%) of the chloro ketone **45b**. A portion of this material was recrystallized from 1-chlorobutane

(22) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(23) Fetscher, C. A.; Bogert, M. T. *J. Org. Chem.* **1939**, *4*, 71.
(24) A commercially available mixture of diphenyl ether and biphenyl, bp 230–250 °C.
(25) Kermack, W. O.; Storey, N. E. *J. Chem. Soc.* **1951**, 1389.
(26) Assignment of the relative configuration of the epoxides **37** and **38** is based on their respective subsequent conversion to the amino alcohols **39** and **40**. Howe[6] has assigned the relative configurations of amino alcohols **39** and **40** from analysis of their NMR spectra. The *R*,R** configuration of amino alcohol **40** was confirmed by solution of its single-crystal structure by X-ray diffraction.[20]
(27) deBoer, T. J.; Backer, H. J. "Organic Syntheses"; Wiley: New York, 1963; p 250.

to give white platelets: mp 167–170 °C dec; NMR ($CDCl_3$) δ 1.44 (t, 3, J = 7 Hz, CH_3), 4.5 (m, 6, OCH_2CHO, CH_2Cl, CH_2CH_3), 5.16 (dd, 1, J = 3.5, 5.4 Hz, OCH_2CHO), 7.73 (s, 1, aromatic H), 8.9 (s, 1, CH=N); IR ($CHCl_3$) 1732 (s), 1584 (m), 1537 (m), 1486 (s), 1447 (s), 1322 (s) cm^{-1}.

Anal. Calcd for $C_{16}H_{12}Cl_3NO_5$: C, 47.49; H, 2.99; N, 3.46. Found: C, 47.83; H, 2.97; N, 3.42.

Ethyl 9,10-Dichloro-3-oxiranyl-2,3-dihydro-1,4-dioxino[2,3-*g*]quinoline-8-carboxylate: *S*,R Diastereoisomer 46b and *R*,R** Diastereoisomer 47b.** A suspension of 2.0 g (4.94 mmol) of the chloro ketone **45b** in 20 mL of ethanol was stirred at 0 °C. To this suspension was added 188 mg (4.94 mmol) of $NaBH_4$ in small portions over 5 min. After an additional 15 min at 0 °C, 1 mL of acetone was added, and the mixture was stirred for an additional 5 min at 0 °C. Extraction with dichloromethane gave a light yellow solid. This solid was dissolved in 50 mL of THF–ethanol (1:1) at 20 °C. To this stirred solution was added 5.43 mL (5.43 mmol) of 1 N NaOH, and stirring was continued for 20 min. Extraction with dichloromethane gave 1.21 g of a light yellow solid. Flash chromatography[22] on silica gel with 20% ether–dichloromethane gave 900 mg (49%) of epoxide isomers. These isomers were separated by medium-pressure chromatography on a 2.5 × 100 cm column of silica gel with 20% ether–dichloromethane. A portion of the more mobile, major isomer **46b**[28] was recrystallized from dichloromethane–ether to give fine white needles: mp 184–185 °C; NMR ($CDCl_3$) δ 1.43 (t, 3, J = 7 Hz, CH_3), 2.93 (m, 2, epoxide CH_2), 3.21 (m, 1, epoxide CH), 4.13 (m, 1, OCH_2CHO), 4.48 (q, 2, J = 7 Hz, OCH_2CH_3), 4.5 (m, 2, OCH_2CHO), 7.60 (s, 1, aromatic H), 8.86 (s, 1, CH=N).

Anal. Calcd for $C_{16}H_{13}Cl_2NO_5$: C, 51.91; H, 3.54; N, 3.78. Found: C, 52.27; H, 3.42; N, 3.71.

A portion of the less mobile, minor isomer was recrystallized from ether to give epoxide **47b**[28] as fine white needles: mp 136–139 °C; NMR ($CDCl_3$) δ 1.43 (t, 3, J = 7 Hz, CH_3), 2.93 (m, 2, epoxide CH_2), 3.28 (m, 1, epoxide CH), 4.4 (m, 3, OCH_2CHO), 4.49 (q, 2, J = 7 Hz, OCH_2CH_3), 7.62 (s, 1, aromatic H), 8.88 (s, 1, CH=N).

(*S*,R)-Ethyl 10-Chloro-3-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-2,3,6,9-tetrahydro-9-oxo-1,4-dioxino[2,3-*g*]quinoline-8-carboxylate (50b).** A suspension of 503 mg (1.36 mmol) of the epoxide **46b** in 20 mL of freshly distilled trifluoroethanol was treated with 712 μL (496 mg, 6.80 mmol) of *tert*-butylamine. This mixture was stirred at room temperature in a sealed flask for 72 h. The reaction mixture was diluted with ethanol, and the solvents were removed by rotary evaporation (30 °C). This was followed by addition and similar removal of a second portion of ethanol. The residue was dissolved in 5 mL of Me_2SO and treated with 0.5 mL of 20% aqueous HCl. The reaction mixture was stirred at 20 °C for 15 min, diluted by slow addition of saturated aqueous $NaHCO_3$ solution, heated briefly to reflux, and then cooled to 0 °C. The tan precipitate was isolated by filtration and dried. This material was suspended in a mixture of dichloromethane and ether (1:1, 20 mL) and stirred for 20 min. The product was reisolated by filtration and amounted to 401 mg (68%) of the quinolone **50b**[28] as a white powder: mp 218 °C dec (rapid heating); NMR (Me_2SO-d_6, 300 MHz) δ 1.08 (s, 9, $(CH_3)_3C$), 1.27 (t, 3, J = 7 Hz, CH_3CH_2), 2.71 (dd, 1, J = 6, 11 Hz, CH_2NH); 2.82 (dd, 1, J = 3, 11 Hz, CH_2NH), 3.33 (br, s, NH, OH), 3.76 (m, 1, CHOH), 4.19 (q, 2, J = 7 Hz, CH_3CH_2), 4.23 (m, 1, OCH_2CHO), 4.29 (m, 1, OCH_2CHO), 4.56 (d, 1, J = 11 Hz, OCH_2CHO), 7.07 (s, 1, aromatic H), 8.39 (s, 1, =CHN).

Anal. Calcd for $C_{20}H_{25}ClN_2O_6 \cdot 0.5H_2O$: C, 55.36; H, 6.04; N, 6.46. Found: C, 55.12; H, 5.93; N, 6.33.

Characterization of the Adduct 52. In the above preparation of amino alcohol **50b**, formation of 15% of a byproduct, which was tentatively assigned structure **52**, was noted. This product was characterized as follows: R_f 0.35 (1% $CH_3OH/CHCl_3$ (NH_3),[29] silica gel; amino alcohol **50b**, R_f 0.44); NMR ($CDCl_3$) δ 1.17 (s, $(CH_3)_3CNH$), 1.40 (t, J = 7 Hz, CH_3CH_2), 4.41 (q, J = 7 Hz, CH_3CH_2), 7.10 (s, NH), 7.38 (s, aromatic H), 9.01 (s, CH=N).

(*R*,R)-Ethyl 10-Chloro-3-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-2,3,6,9-tetrahydro-9-oxo-1,4-dioxino[2,3-*g*]quinoline-8-carboxylate (51b).** Treatment of 367 mg (1.02 mmol) of epoxide **47b** as described above gave 278 mg (64%) of the quinolone **51b**[28] as a white powder: NMR (Me_2SO-d_6, 300 MHz) δ 1.05 (s, 9, $(CH_3)_3C$), 1.26 (t, 3, J = 7 Hz, CH_3CH_2), 2.72 (br m, 2, CH_2N), 3.33 (br s, OH, NH), 3.73 (br m, 1, CHOH), 4.18 (q, 2, J = 7 Hz, CH_3CH_2), 4.18 (br m, 1, OCH_2CHO), 4.33 (br m, 1, OCH_2CHO), 4.56 (d, 1, J = 11 Hz, OCH_2CHO), 7.04 (s, 1, aromatic H), 8.39 (s, 1, =CHN).

Anal. Calcd for $C_{20}H_{25}ClN_2O_6 \cdot H_2O$: C, 54.23; H, 6.15; N, 6.33. Found: C, 54.34; H, 5.82; N, 5.97.

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Registry No. 2, 54340-59-9; **10b**, 28387-13-5; **11b**, 50352-33-5; **12a**, 78265-45-9; **12b**, 78265-46-0; **13**, 78265-47-1; **14**, 78265-48-2; **15a**, 59987-31-4; **15b**, 78265-49-3; **16a**, 78265-50-6; **16b**, 78265-51-7; **17a**, 78265-52-8; **17b**, 78265-53-9; **18**, 78265-54-0; **20**, 3663-82-9; **20** acetate, 64179-44-8; **23**, 50352-43-7; **25a**, 78265-55-1; **25b**, 78265-56-2; **26a**, 78265-57-3; **26b**, 78265-58-4; **27a**, 78265-59-5; **27b**, 78265-60-8; **28**, 78265-61-9; **29**, 78265-84-6; **30**, 13720-94-0; **33**, 78265-62-0; **36**, 1014-19-3; **37**, 78339-59-0; **38**, 78339-60-3; **39**·HCl, 78265-63-1; **40**·HCl, 78265-64-2; **41a**, 78265-65-3; **42a**, 78265-66-4; **42b**, 78265-67-5; **43a**, 78265-68-6; **43b**, 78265-69-7; **44a**, 78279-89-7; **44b**, 78265-70-0; **45a**, 78265-71-1; **45b**, 78265-72-2; **46a**, 78265-73-3; **46b**, 78265-74-4; **47a**, 78265-75-5; **47b**, 78265-76-6; **48a**, 78265-77-7; **49a**, 78265-78-8; **50a**, 78265-79-9; **50b**, 78265-80-2; **51a**, 78265-81-3; **51b**, 78265-82-4; **52**, 78265-83-5; 4-nitrocatechol, 3316-09-4; benzyl chloride, 100-44-7.

Supplementary Material Available: Complete and expanded experimental data for the other compounds indicated in the schemes (24 pages). Ordering information is given on any current masthead page.

(28) Assignment of the relative configurations of amino alcohols **48–51** is based on comparison of their NMR spectra with those reported by Howe[6] for the amino alcohols **39** and **40**. Assignments for the epoxides **46** and **47** are based on their subsequent conversion to the above amino alcohols.

(29) "Chloroform (NH_3)" as a TLC or chromatography solvent was prepared by shaking chloroform with concentrated ammonium hydroxide. The chloroform layer was isolated and then used to prepare the indicated solvent mixtures.