at 200.[23] The retention time was 1.3 min for **23** and 2.0 min for **24**.

B. Acid Chloride Aminolysis.—Carboxylic acids **11** and **12** were separately converted to their resp halides using $SOCl_2$ in C_6H_6. The addn of aq $HNMe_2$ to the crude acid chloride afforded an aq soln of the amide which was continuously extd with Et_2O for 24 hr. Evapn of the dry Et_2O ext afforded the amide which was chromatographed on silica gel, and then distd evaporatively. *Anal.* ($C_9H_{15}NO_2$) C, H, N.

Exo amide **24** was prepared from **12** by a similar procedure. *Anal.* ($C_9H_{15}NO_2$) C, H, N.

***endo*-2-(*N*,*N*-Dimethylamino)methyl-7-oxabicyclo[2.2.1]heptane Methiodide (4) (25).**—Amide **23** was reduced by the method described for redn of carbamate **17**, affording amine **25** as an oil in 85% yield which was converted to **4** (85%) by the method described for **2**, mp 274–275° (Me_2CO–MeOH). *Anal.* ($C_{10}H_{20}INO$) C, H, N.

Exo amine **26** was prepd from **24** by LAH redn (75%) and converted to **5** (70%), mp 233–234° (Me_2CO–MeOH). *Anal.* ($C_{10}H_{20}INO$) C, H, N.

Pharmacological Testing.—Compds were tested on isolated guinea pig ileum perfused in a 5-ml chamber at 37° with the physiol soln described by Blinks and Koch-Weser.[25] Generally, test compds were dissolved at a concn of 10^{-1} *M* in this soln. Appropriate amts were then added to achieve a given final concn in the tissue bath. Concn–effect curves were detd for each compd, and for ACh by exposing the tissue to the drug for 30 sec and then washing out the drug at least 4 times. The max contraction occurring during the 30-sec exposure was taken as the response. The interval between exposure to different concns of a given compd, or to different compds was not less than 4 min. In each tissue preparation a maximal (100%) contraction was defined as that isotonic contraction produced by 10^{-5} *M* ACh. All other response were then expressed as a percentage of the maximal contraction of the tissue as so defined.

At least 3, and usually 5 or more separate experiments (tissues) were employed for each compd at various concns. One exception was **2** at 10^{-2} *M*, where only 2 experiments were performed. When more than one response was elicited in a given tissue, with a given concn of a particular compd the individual responses were averaged and were counted as 1 observation. Observations from sep experiments (tissues) were then averaged and the standard error of the mean was calcd using standard statistical methods for small groups.

For each compd the concn producing a 50% contraction ($[X]_{50}$) was estimated from the standard semilog plot of the concn–effect data.

To test for possible nicotinic actions each compd was tested in the presence of 10^{-5} *M* hexamethonium which was added 1 min prior to the test compd. This concn of hexamethonium blocked the response to dimethylphenylpiperazinium iodide (DMPP) (10^{-6} *M*). To test for possible atropine-like action of the compds another procedure was employed. A low, or just no effect, concn of the test compd was introduced for 1 min, followed by a test dose of 10^{-7} *M* ACh. The resulting response was compared with the response to 10^{-7} *M* ACh in the absence of the compd. None of the compds exhibited significant atropine-like action in the concns tested.

The muscarinic nature of the responses was determined by treating prepns with 10^{-7} *M* atropine. In the presence of atropine, responses to **2**, **3**, **4**, **5**, and ACh were completely blocked.

Acknowledgment.—The authors gratefully acknowledge the support of the National Institute of Neurological Diseases and Stroke, U. S. Public Health Service, for support of this work, and wish to thank Mrs. Patricia K. Peterson and Miss Mary E. Winkelman for their technical assistance in the muscarinic assays.

(25) J. R. Blinks and J. Koch-Weser, *J. Pharmacol. Exp. Ther.*, **134**, 373 (1961).

Conformational Study of Catecholamine Receptor Sites. 7. Syntheses of *erythro*- and *threo*-3-Amino-2-(3,4-dihydroxyphenyl)-2-butanol Hydrochlorides and *erythro*- and *threo*-2-Amino-3-(3,4-dihydroxyphenyl)butane Hydrochlorides[1]

EDWARD E. SMISSMAN* AND RONALD T. BORCHARDT[2]

Department of Medicinal Chemistry, School of Pharmacy, The University of Kansas, Lawrence, Kansas 66044

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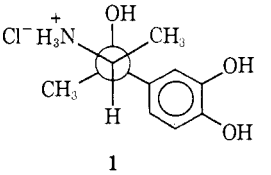
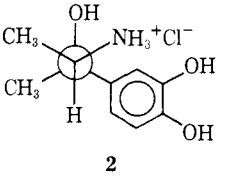
The syntheses of the semirigid analogs of norepinephrine, *threo*- and *erythro*-3-amino-2-(3,4-dihydroxyphenyl)-2-butanol·HCl (**1**, **2**), and the analogs of dopamine, *erythro*- and *threo*-2-amino-3-(3,4-dihydroxyphenyl)butane·HCl (**3**, **4**), are described. The results of O-methylation by catechol-*O*-methyltransferase (COMT) of these norepinephrine and dopamine analogs are discussed.

In earlier publications[3,4] the synthesis and preliminary testing of the decalin analogs of α-methylnorepinephrine and α-methyldopamine were reported. The rigid analogs of α-methylnorepinephrine exhibited marked differences as substrates for catechol-*O*-methyltransferase (COMT), whereas, the differences in activity of the α-methyldopamine analogs were significantly less. These findings indicated a primary role for the β-OH group in the determination of the preferred conformation for COMT activity. To explore further the importance of the β-OH group and the preferred conformations of α-methylnorepinephrine and α-methyldopamine on COMT activity, the synthesis and preliminary testing of the semirigid analogs **1**, **2**, **3**, and **4** were undertaken and are the subject of this paper.



1



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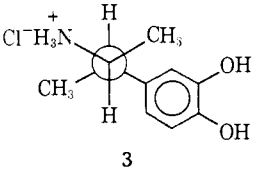

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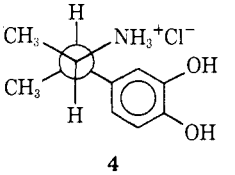


4

(1) Presented in part before the 90th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, Japan, July 29, 1970.

(2) Taken in part from the dissertation presented by R. T. Borchardt, April 1970, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

(3) E. E. Smissman and R. T. Borchardt, *J. Med. Chem.*, **14**, 377 (1971).

(4) E. E. Smissman and R. T. Borchardt, *ibid.*, **14**, 383 (1971).

Semirigid Analogs of α-Methylnorepinephrine.—The synthesis of **1** and **2** was initiated with the acetylation of pyrocatechol[5] to yield **5**, which was subjected to Fries rearrangement[6] to afford **6**. The highly reactive catechol OH's were protected by the reaction of **6** with $PhCH_2Cl$ and K_2CO_3 in Me_2CO to afford the desired ether, 3,4-dibenzyloxyacetophenone (**7**).

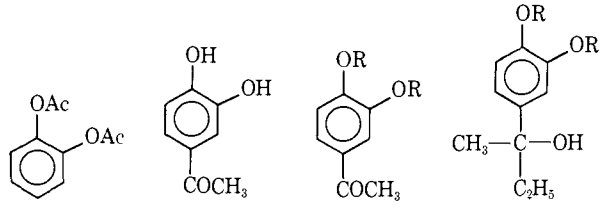
The reaction of **7** with EtMgI resulted in the formation of the alcohol **8**, which on dehydration, utilizing $MgSO_4$ in PhH at room temp, afforded the cis olefin **9** as the exclusive product. No detectable amount of *trans*-2-(3,4-dibenzyloxyphenyl)-2-butene (**10**) was observed. The assignment of the cis configuration to **9** is based on the uv and nmr data, as compared to the previously reported data[7] for the related *cis*- and *trans*-2-phenyl-2-butenes (Table I). The synthesis

TABLE I

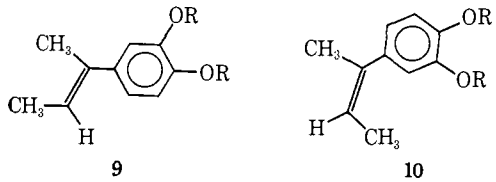
Olefin	Uv, nm λmax	Uv, nm log ε	Nmr, δ C1-Me	Nmr, δ C4-Me
cis-2-Phenyl-2-butene	243[a]	4.082	2.01	1.75
trans-2-Phenyl-2-butene	235[a]	3.912	2.03	1.58
cis-2-(3,4-Dibenzyloxyphenyl)-2-butene (**9**)	257	4.041	1.97	1.75
trans-2-(3,4-Dibenzyloxyphenyl)-2-butene (**10**)	245		1.98	1.53

[a] D. J. Cram, *J. Amer. Chem. Soc.*, **71**, 3883 (1949).

of the trans olefin **10** is reported later in this publication.



5 **6** **7** **8**

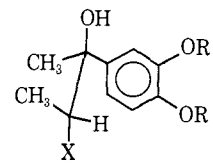


9 **10**

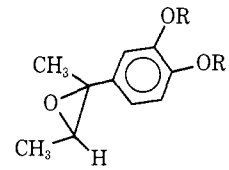
R = $CH_2C_6H_5$

Using NBS as the source of Br, the cis olefin **9** was converted to bromohydrin **11** which on treatment with liq NH_3 at room temp, produced the cis epoxide, **12**. Amination of **12** using NH_3 at elevated temp afforded the threo amino alcohol which was isolated as the HCl salt **13**. Evidence that amination resulted in attack at the least-substituted C-3 position was obtained by conversion of **13** to the *N*-Ac deriv **14**. The ir spectrum of **14** showed OH absorption at 3330 cm^{-1} and $CONH_2$ absorption at 1640 cm^{-1}.

The removal of the benzyl ether protecting groups from **13** was achieved by hydrogenation over 10% Pd/C catalyst to yield *threo*-3-amino-2-(3,4-dihydroxyphenyl)-2-butanol·HCl (**1**).



11, X = Br
13, X = NH_2·HCl
14, X = NHAc

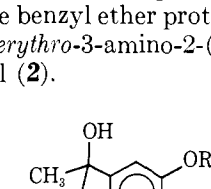


12

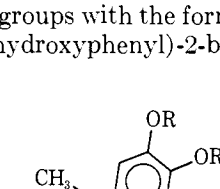
A key intermediate in the synthesis of the erythro amino alcohol **2** was the erythro diol **15**. Oxidation of the cis olefin **9** with OsO_4 or treatment of the cis epoxide **12** with 0.02 *N* H_2SO_4 in aq DMSO afforded the desired erythro diol **15**. The structural assignment of **15** is based on the observation[8] that oxidation of olefins with OsO_4 results in the formation of cis 1,2-diols. Formation of **15** from the acid-catalyzed opening of **12** indicates an intermediate carbonium ion with resulting formation of the more stable erythro diol **15**. This stability can be rationalized by intramolecular H bonding.

Treatment of **15** with $MeSO_2Cl$ in pyridine at 0° afforded the monomesylate **16** which was converted to the trans epoxide **17** utilizing liq NH_3 at room temp. Amination of **17** using NH_3 at elevated temp and pressure resulted in formation of the desired erythro amino alcohol which was isolated as the HCl salt **18**.

Catalytic hydrogenation of **18** resulted in the removal of the benzyl ether protecting groups with the formation of *erythro*-3-amino-2-(3,4-dihydroxyphenyl)-2-butanol ·HCl (**2**).



15, X = OH
16, X = OSO_2CH_3
18, X = NH_2·HCl

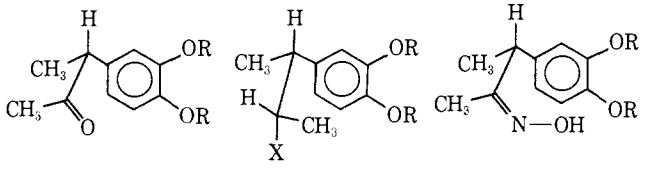


17

Semirigid Analogs of α-Methyldopamine.—The synthesis of the α-methyldopamine analogs **3** and **4** was initiated with the preparation of ketone **19**. The treatment of the erythro diol **15** with a catalytic amount of *p*-TsOH in benzene at reflux or oxidation of the threo alcohol **20**, according to the general procedure of Pfitzner and Moffatt,[9] afforded the ketone **19**. The alcohol **20** was prepared by the hydroboration of the cis olefin **9**. Since diborane addition is a cis addition and oxidation of the intermediate alkylborane with H_2O_2 occurs with retention of configuration,[10] the alcohol **20** was assigned the threo configuration.

The ketone **19** was converted to the corresponding oxime **21**. Metal hydride reduction of oxime **21** was expected to afford a mixture of amines **22** and **23**. According to Cram's rule of steric control,[11] the threo amine **22** was predicted to be the major isomer and the erythro amine **23** the minor isomer.

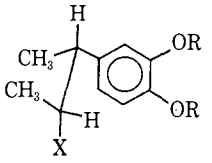
(5) G. Heller, P. Lindner, and H. George, *Chem. Ber.*, **56**, 1871 (1923).
(6) M. D. Moed, J. Van Dijkand, and H. Niewind, *Recl. Trav. Chim. Pays-Bas*, **77**, 273 (1958).
(7) D. J. Cram, *J. Amer. Chem. Soc.*, **71**, 3883 (1949).
(8) F. D. Gunstone, *Advan. Org. Chem.*, **1**, 103 (1960).
(9) E. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5670 (1965).
(10) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963).
(11) D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem. Soc.*, **74**, 5828 (1952).



19 **20**, X = OH; **22**, X = NH_2·HCl; **24**, X = OSO_2CH_3 **21**

R = $CH_2C_6H_5$

LAH reduction of oxime **21** resulted in a mixture (75:25) of the desired amines **22** and **23**, respectively. Poor yields and difficulty in the separation of products from this reaction led to the investigation of more stereospecific reactions.



23, X = NH_2·HCl
25, X = N_3

Sodium bis(2-methoxyethoxy)aluminum hydride reduction of oxime **21**, according to the general procedure of Bazant,[12] resulted in formation of the threo amine which was isolated as the HCl salt **22**. No detectable amount of the corresponding erythro isomer **23** was observed. Removal of the benzyl ether protecting groups from **22** was achieved by catalytic hydrogenation to yield the desired *threo*-2-amino-3-(3,4-dihydroxyphenyl)butane·HCl (**4**).

A stereospecific synthesis of the erythro amine **3** was achieved by utilizing the threo alcohol **20**. The treatment of **20** with MsCl in pyridine afforded the mesylate **24** which on displacement using NH_3 at elevated temp and pressure resulted in poor yields of the erythro amine **23**. A major side product from the reaction was *trans*-2-(3,4-dibenzyloxyphenyl)-2-butene (**10**), which was formed by a trans elimination of the mesylate function.

The problem of elimination and formation of the trans olefin **10** was minimized by displacement of the mesylate function using N_3^-. Treatment of **24** with NaN_3 in DMF at elevated temp afforded the desired erythro azide **25**, which on LAH reduction resulted in the formation of the desired erythro amine which was isolated as the HCl salt **23**. Amine **23** was shown to be identical in all respects with the minor product obtained from the LAH reduction of the oxime **21**.

Catalytic hydrogenation of **23** resulted in the removal of the benzyl ether protecting groups and afforded the *erythro*-2-amino-3-(3,4-dihydroxyphenyl)butane·HCl (**3**).

Biological Results.—Table II lists the observed rates and relative rates of O-methylation by catechol-*O*-methyltransferase[3,13] (COMT) of the α-methylnorepinephrine analogs **1** and **2**, the α-methyldopamine analogs **3** and **4**, dopamine, and L-norepinephrine. Table III lists the K_m, V_{max}, and relative V_{max} determined for the same substrates.

TABLE II
CATECHOL-*O*-METHYLTRANSFERASE.[a]
RATES OF O-METHYLATION OF α-METHYLNOREPINEPHRINE AND α-METHYLDOPAMINE ANALOGS

Compd	Configuration	nmoles of product/10 min[d]	Relative rates
1[b]	Threo	9.87	1.41
2[b]	Erythro	17.54	2.49
3[b]	Erythro	24.88	3.54
4[b]	Threo	11.71	1.67
Dopamine[b]		28.41	4.04
L-Norepinephrine[c]		7.03	1.00

[a] Assay conditions. The assay mixt contd the following components (in μmoles) added in this sequence: H_2O, so that the final vol was 0.5 ml; $MgCl_2$ (1.0); sodium phosphate buffer, pH 8.0 (50); *S*-adenosyl-L-methionine (0.5); 0.1 μCi of *S*-adenosyl-L-methionine-^{14}C and substrate (0.1). Final substrate concn was 2.0×10^{-4} *M*. Enzyme prepn, purified by procedure of B. Nikadejevic, S. Senoh, J. W. Daly, and C. R. Creveling, *J. Pharmacol. Exp. Ther.*, **174**, 83 (1970), contd 8.7 mg of protein/ml. The reaction was started by the addn of substrate and incubated for 10 min at 37°. The reaction was stopped by addn of 0.5 ml of 0.5 *M* borate buffer, pH 10.0, and the mixt was extd with 10 ml of PhMe–*i*-AmOH (3:2). Following centrifugation, an aliquot (5 ml) of the org phase was transferred to a scintillation vial, a dioxane-based phosphor soln (10 ml) was added, and the radioactivity was measured in a scintillation spectrophotometer. The results were corrected for blank values obtained by carrying out the reaction without substrate. [b] HCl salt. [c] Bitartrate salt. [d] 0.1 ml of enzyme/assay.

TABLE III
CATECHOL-*O*-METHYLTRANSFERASE.[a]
K_m AND V_{max} OF α-METHYLNOREPINEPHRINE AND α-METHYLDOPAMINE ANALOGS

Compd	Configuration	K_m[e] × 10^{-4}	V_{max}, nmoles of product/10 min[d]	Relative V_{max}
1[b]	Threo	5.62	37.1	0.37
2[b]	Erythro	8.95	101.5	1.01
3[b]	Erythro	16.7	167.2	1.68
4[b]	Threo	19.9	128.9	1.29
Dopamine[b]		7.77	136.9	1.37
L-Norepinephrine[c]		26.2	99.7	1.00

[a] Assay conditions. The assay procedure was identical with that described in Table II except that final substrate concns ranged from 3.0×10^{-4} to 0.4×10^{-4} *M*. The K_m and V_{max} values were obtd from a least-squares analysis of plotting $1/V$ *vs.* $1/S$. [b] HCl salt. [c] Bitartrate salt. [d] 0.1 ml of enzyme/assay. [e] Correlation coefficients > 0.997.

In the α-methylnorepinephrine series the preferred conformation for the COMT site appears to be that where the NH_2, OH, and Ar groups are gauche as shown by the activity of the erythro isomer **2**. The activity of **2** correlates well with the activity observed for 3(e)-amino-2(e)-(3,4-dihydroxyphenyl)-*trans*-2(a)-decalol·HCl,[3] which has the same relative conformation.

In the α-methyldopamine series the preferred conformation for the COMT site appears to be that where the NH_2 and Ar groups are completely staggered as shown by the activity of the erythro isomer **3**. The activity of **3** again correlates well with the activity observed for 3(a)-amino-2(a)-(3,4-dihydroxyphenyl)-*trans*-decalin·HCl,[4] which has a fixed staggered conformation.

(12) V. Bazant, M. Capka, M. Cerny, V. Chvalovsky, K. Kockloefl, M. Kraus, and J. Malek, *Tetrahedron Lett.*, 3303 (1968).
(13) B. Nikadejevic, S. Senoh, J. W. Daly, and C. R. Creveling, *J. Pharmacol. Exp. Ther.*, **174**, 83 (1970).

The high substrate specificity observed for the α-methylnorepinephrine analogs in the *trans*-decalin series[3] was not as apparent in the butane series. This may be due to the fact that the butane analogs **1** and **2** do not possess completely fixed conformations as in the decalin series and one thus loses some of the conformational specificity. It should also be noted that the conformation where the amino and OH groups have a dihedral angle of 180°, which possessed the very high activity in the decalin series,[3] is not represented in the butane analogs. The conformations depicted by the Newman projections for **1** and **2** are based by analogy to the preferred conformations of ephedrine and ψ-ephedrine reported by Portoghese. He showed that in a variety of solvents, the ephedrines are intramolecularly H bonded both as the free bases and salts.[14] With the erythro isomer **3**, J_{ab} = 7.7 Hz and in the threo isomer **4**, J_{ab} = 9.3 Hz in D_2O. These data indicate the protons to be in a staggered conformation as opposed to a gauche form.

Experimental Section†

Pyrocatechol Diacetate (**5**).—Commercially available pyrocatechol (60.0 g, 0.545 mole) was acetylated by the method of Heller and coworkers[5] utilizing Ac_2O to yield 90.4 g (86%) of **5**, mp 61–63° (lit.[5] 63.5°).

3,4-Dihydroxyacetophenone (**6**).—The method of Moed[6] using pyrocatechol diacetate (**5**) (66.0 g, 0.294 mole) and $AlCl_3$ (133.3 g, 1.00 mole) and C_6H_5Cl as a solvent afforded the desired **6**: 34.5 g (78%); mp 117–118° (lit.[6] 118–119°).

3,4-Dibenzyloxyacetophenone (**7**).—To a soln of 3,4-dihydroxyacetophenone (**6**) (45.00 g, 0.30 mole) in 900 ml of Me_2CO under N_2 was added anhyd K_2CO_3 (99.00 g, 0.72 mole) and $PhCH_2Cl$ (90.90 g, 0.72 mole). The reaction mixt was stirred for 4 days under reflux. After cooling to 25°, the solids were removed by filtration and washed several times with Me_2CO. The combined Me_2CO fractions were concd *in vacuo* to yield a semisolid mass which was dissolved in 1 l. of C_6H_6. The C_6H_6 soln was washed with 1 *N* NaOH, satd NaCl soln, and H_2O. The C_6H_6 soln was dried ($MgSO_4$) and the C_6H_6 was removed *in vacuo* to afford 94.0 g of cryst material. Recrystn ($CHCl_3$–hexane) afforded 82.4 g (82.5%) of **7**, mp 93–95°. *Anal.* ($C_{22}H_{20}O_3$) C, H.

***cis*-2-(3,4-Dibenzyloxyphenyl)-2-butene** (**9**).—To Mg turnings (2.19 g, 0.09 g-atom) under N_2 was added EtI (14.04 g, 0.09 mole) in 100 ml of anhyd Et_2O at such a rate as to maintain reflux. The reaction mixt was stirred at 25° for 3 hr after which 3,4-dibenzyloxyacetophenone (**7**) (20.6 g, 60 mmoles) in 150 ml of anhyd C_6H_6 was added at such a rate as to maintain reflux. The reaction mixt was stirred at 25° for 4 hr after which a soln of satd NH_4Cl was added dropwise. The resulting aq soln was washed several times with C_6H_6 and the combined C_6H_6 fractions were washed with satd NH_4Cl soln and H_2O. To the C_6H_6 soln was added 10 g of anhyd $MgSO_4$ and the resulting soln was stirred at 25° for 16 hr. The desiccant was removed by filtration and the C_6H_6 was removed *in vacuo* to yield 22.4 g of a reddish oil. Crystn (hexane) afforded 15.85 g (78%) of **9**, mp 57.5–59.5°. *Anal.* ($C_{24}H_{24}O_2$) C, H.

***threo*-3-Amino-2-(3,4-dibenzyloxyphenyl)-2-butanol·HCl** (**13**).—To *cis*-2-(3,4-dibenzyloxyphenyl)-2-butene (**9**) (2.50 g, 7.3 mmoles) in 50 ml of dioxane was added a soln of H_2SO_4 (0.75 g, 7.7 mmoles) in 5 ml of H_2O while cooling the reaction mixt in an ice bath. The temp of the mixt was maintained at 10–15° during the addition of NBS (1.33 g, 7.7 mmoles) in 15 ml of dioxane. After stirring the mixt for 6 hr at 10–15°, H_2O was added. The aq soln was extd several times with Et_2O and the combined Et_2O fractions were washed with satd NaCl soln and H_2O. The Et_2O soln was dried ($MgSO_4$) and the Et_2O was removed to afford 3.2 g of **11**, a yellowish oil.

The crude bromohydrin was placed in a steel reaction vessel cooled in a Dry Ice–Me_2CO bath and *ca.* 100 ml of liq NH_3 was added. The vessel was sealed and allowed to remain at 25° for 24 hr after which it was heated at 155° for 30 hr. After cooling the vessel in a Dry Ice–Me_2CO bath, the pressure was released and the NH_3 allowed to evap. The residue was dissolved in $CHCl_3$ and filtered to remove solid impurities. The $CHCl_3$ was removed to afford 2.7 g of a reddish oil. Chromatog on silica gel by eluting with 5% MeOH–$CHCl_3$ afforded 1.50 g of a colorless oil. Formation of the HCl salt and recrystn (abs EtOH) afforded 0.95 g (32%) of **13**, mp 226–227°. *Anal.* ($C_{24}H_{28}ClNO_3$) C, H, N.

***threo*-*N*-Acetyl-3-amino-2-(3,4-dibenzyloxylphenyl)-2-butanol** (**14**).—To AcOH (1 ml), NaOAc (50 mg), and *threo*-3-amino-2-(3,4-dibenzyloxyphenyl)-2-butanol·HCl (**13**) (0.100 g, 0.25 mmole) was added Ac_2O (2 ml). The reaction mixt was allowed to stir for 2 hr at 25°, after which H_2O was added and the excess Ac_2O was allowed to decomp. The H_2O layer was washed several times with EtOAc. The combined EtOAc fractions were washed with H_2O, 5% HCl soln, and satd NaCl soln. The EtOAc soln was dried ($MgSO_4$) and the solvent was removed to afford 0.082 g of a semisolid product. Thick-layer chromatog on silica gel by eluting with 2% MeOH–$CHCl_3$ afforded on recrystn (Et_2O) 0.034 g (33%) of **14**: mp 120–121°; ir (KBr) 3330 (OH), 1640 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.50–6.85 (m, 13 H, arom), 5.15 (s, 4 H, benzylic), 3.97 (q, 1 H, C-3 C**H**), 1.93 (s, 3 H, amide C**H**$_3$), 1.51 (s, 3 H, C-1 C**H**$_3$), 0.90 (d, 3 H, C-4 C**H**$_3$). *Anal.* ($C_{26}H_{29}NO_4$) C, H, N.

***threo*-3-Amino-2-(3,4-dihydroxyphenyl)-2-butanol·HCl** (**1**).—To *threo*-3-amino-2-(3,4-dibenzyloxyphenyl)-2-butanol·HCl (**13**) (1.035 g, 2.5 mmoles) in 30 ml of anhyd MeOH was added 275 mg of 10% Pd/C under N_2. The reaction mixt was hydrogenated at 25° under atm pressure. The reaction was stopped after consumption of the theoretical amount of H_2. The catalyst was removed by filtration and the solvent was removed. The resulting solid was recrystd (MeOH–Et_2O) to yield 0.566 g (95%) of **1**: mp 186–189°; nmr (CD_3OD) δ 7.11–6.87 (m, 3 H, arom), 4.18 (q, 1 H, C-3 C**H**), 1.65 (s, 3 H, C-1 C**H**$_3$), 0.96 (d, 3 H, C-4 CH_3). *Anal.* ($C_{10}H_{16}ClNO_3$) C, H, N.

***cis*-2-(3,4-Dibenzyloxyphenyl)butane 2,3-Oxide** (**12**).—To *cis*-2-(3,4-dibenzyloxyphenyl)-2-butene (**9**) (2.50 g, 7.3 mmoles) in 50 ml of dioxane was added a soln of H_2SO_4 (0.750 g, 7.7 mmoles) in 5 ml of H_2O while cooling the reaction mixt in an ice bath. The temp of the mixt was maintained at 10–15° during the addn of NBS (1.22 g, 7.7 mmoles) in 15 ml of dioxane After stirring the mixt for 6 hr at 10–15°, H_2O was added The H_2O soln was extd several times with Et_2O and the combined Et_2O fractions were washed with satd NaCl soln and H_2O. The Et_2O soln was dried ($MgSO_4$) and the Et_2O was removed to afford a yellowish oil, 3.2 g.

The crude bromohydrin **11** was placed in a steel reaction vessel cooled in a Dry Ice–Me_2CO bath and *ca.* 100 ml of liq NH_3 was added. The vessel was sealed and allowed to remain at 25° for 24 hr. After cooling the vessel in a Dry Ice–Me_2CO bath, the pressure was released and the NH_3 allowed to evap. The residue was dissolved in $CHCl_3$ and filtered to remove solid impurities. The $CHCl_3$ was removed to afford 2.45 g of a colorless gum: ir (neat) 1205 cm^{-1} (epoxide; nmr ($CDCl_3$) δ 7.55–6.85 (m, 13 H, arom), 5.10 (s, 4 H, benzylic), 2.85 (q, 1 H, C-3 C**H**), 1.53 (s, 3 H, C-1 CH_3), 1.33 (s, 3 H, C-4 C**H**$_3$). The crude cis epoxide **12** was utilized without further purification.

***erythro*-2-(3,4-Dibenzyloxyphenyl)butane-2,3-diol** (**15**). **A. From *cis*-2-(3,4-Dibenzyloxyphenyl)-2-butene** (**9**).—To a soln of OsO_4 (1.00 g, 3.94 mmoles) in 15 ml of anhyd THF was added a soln of *cis*-2-(3,4-dibenzyloxyphenyl)-2-butene (**9**) (1.27 g, 3.60 mmoles) in 15 ml of anhyd THF and 1 ml of anhyd C_6H_5N. The reaction mixt was stirred at 25° for 24 hr after which 20 ml of anhyd Et_2O was added. H_2S was bubbled through the reaction mixt, and the black ppt formed was removed by filtration. The Et_2O was removed *in vacuo* to afford a reddish oil which crystd after the addition of a few drops of EtOAc. Recrystn ($CHCl_3$–hexane) afforded 0.910 g (67%) of **15**: mp 84–85.5°; ir (KBr) 3330 cm^{-1} (O-H); nmr ($CDCl_3$) δ 7.65–6.92 (m, 13 H, arom), 5.15 (s, 4 H, benzylic), 3.89 (q, 1 H, C-3 C**H**), 1.41 (s, 3 H, C-1 C**H**$_3$), 1.04 (d, 3 H, C-4 C**H**$_3$). *Anal.* ($C_{24}H_{26}O_4$) C, H.

B. From *cis*-2-(3,4-Dibenzyloxyphenyl)butene 2,3-Oxide (**12**).

† Melting points were obtained on a calibrated Thomas-Hoover Uni-Melt and are corrected. Ir data were recorded on Beckman IR10 and Perkin-Elmer 421 spectrophotometers, and nmr data on a Varian Associates Model A-60 A spectrophotometer (TMS). Microanalyses were conducted by Midwest Microlab, Inc., Indianapolis, Ind., on an F and M Model 185 C, H, N Analyzer, University of Kansas, Lawrence, Kan., and Microanalytical Laboratory, National Institutes of Health, Bethesda, Md. Where analyses are indicated only by symbols of the elements, anal. results obtained for these elements were within ± 0.4% of the theoretical values.

(14) P. S. Portoghese, *J. Med. Chem.*, **10**, 1057 (1967).

—To *cis*-2-(3,4-dibenzyloxyphenyl)butene 2,3-oxide (**12**) (2.35 g, 7.3 mmoles) dissolved in 225 ml of DMSO was added dropwise a soln of 75 ml of H_2O and H_2SO_4 (0.300 g, 3.0 mmoles) final concn, 0.02 *N* H_2SO_4). The reaction mixt was stirred at 25° for 3 hr after which H_2O was added. The aq soln was extd several times with C_6H_6 and the combined C_6H_6 fractions were washed with H_2O and satd NaCl soln. The C_6H_6 soln was dried ($MgSO_4$) and the C_6H_6 was removed to afford 2.35 g of a colorless oil. Chromatog on silica gel by eluting with $CHCl_3$ afforded, after recrystn (Me_2CO–hexane), 1.55 g (56%) of **15**, mp 84–85.5°.

erythro-**3-Amino-2-(3,4-dibenzyloxyphenyl)-2-butanol·HCl** (**18**).—To *erythro*-2-(3,4-dibenzyloxyphenyl)butane-2,3-diol (**15**) (1.00 g, 2.7 mmoles) in 12 ml of anhyd C_6H_5N, cooled in an ice bath, was added $MeSO_2Cl$ (0.500 g, 4.4 mmoles) in 2 ml of anhyd C_6H_5N. The reaction mixt was allowed to remain in the freezer for 16 hr after which H_2O was added. The aq soln was extd several times with Et_2O and the combined Et_2O fractions were washed with H_2O and satd NaCl soln. The Et_2O soln was dried ($MgSO_4$) and the Et_2O was removed to yield 1.20 g of **16**, a colorless gum.

The crude mesylate was placed in a steel reaction vessel cooled in a Dry Ice–Me_2CO bath and *ca.* 100 ml of liq NH_3 was added. The vessel was sealed and allowed to remain at 25° for 16 hr after which it was heated at 150–160° for 36 hr. After cooling in a Dry Ice–Me_2CO bath the vessel was opened and the NH_3 was allowed to evap. The residue was dissolved in $CHCl_3$ and filtered, and the $CHCl_3$ soln was dried ($MgSO_4$). The $CHCl_3$ was removed to yield 1.05 g of a dark red oil. Chromatog on silica gel, eluting with 5% MeOH–$CHCl_3$, afforded 0.750 g of a colorless oil. Formation of the HCl salt and recrystn (EtOH–Et_2O) afforded 0.502 g (44.5%) of **18**, mp 157–159°. *Anal.* ($C_{24}H_{28}ClNO_3$) C, H, N.

erythro-**3-Amino-2-(3,4-dihydroxyphenyl)-2-butanol·HCl** (**2**).—To *erythro*-3-amino-2-(3,4-dibenzyloxyphenyl)-2-butanol·HCl (**18**) (1.00 g, 2.41 mmoles) in 30 ml of anhyd MeOH was added 275 mg of 10% Pd/C under N_2. The reaction mixt was hydrogenated at 25° under atm pressure. The reaction was stopped after consumption of the theor amt of H_2. The catalyst was removed by filtration and the solvent removed *in vacuo*. The resulting solid was recrystd (EtOH–Et_2O) to yield 0.505 g (90%) of **2**: mp 180–182°; nmr (CD_3OD) δ 7.14–6.83 (m, 3 H, arom), 3.48 (q, 1 H, C-3 CH), 1.55 (s, 3 H, C-1 C**H**$_3$), 1.28 (d, 3 H, C-4 C**H**$_3$). *Anal.* ($C_{10}H_{16}ClNO_3$) C, H, N.

threo-**3-(3,4-Dibenzyloxyphenyl)-2-butanol** (**20**).—To a soln of $NaBH_4$ (0.102 g, 2.69 mmoles) and *cis*-2-(3,4-dibenzyloxyphenyl)-2-butene (**9**) (2.060 g, 6.00 mmoles) in 30 ml of anhyd diglyme was added dropwise a soln of $BF_3·Et_2O$ (0.510 g, 3.60 mmoles) in 10 ml of Diglyme. The reaction mixt was cooled to maintain the temp at *ca.* 20° during addition. It was stirred at 25° for 1 hr after which 3 ml of H_2O was added dropwise to decomp the excess hydride. The intermediate organoborane was oxidized at 35° by the immediate addition of 4 ml of 3 *N* NaOH followed by dropwise addition of 4 ml of 30% H_2O_2 soln. The reaction mixt was stirred for 2 hr at 25° and then extd with 100 ml of Et_2O. The ethereal ext was washed 5 times with equal amts of ice H_2O to remove Diglyme and dried ($MgSO_4$) after which the solvent was removed to yield a colorless oil, 2.20 g. Chromatog on silica gel, eluting with $CHCl_3$, afforded 1.82 g (85%) of **20**, a colorless oil: ir (neat) 3520 cm^{-1} (OH); nmr ($CDCl_3$) δ 7.65–7.18 (m, 13 H, arom), 5.20 (s, 2 H, benzylic), 5.15 (s, 2 H, benzylic), 3.71 (m, 1 H, C-2 C**H**), 2.62 (m, 1 H, C-3 C**H**), 1.20 (d, 3 H, C-1 C**H**$_3$), 1.13 (d, 3 H, C-4 C**H**$_3$). Analysis obtained on mesylate derivative **24**.

3-(3,4-Dibenzyloxyphenyl)-2-butanone (**19**). **A. From *erythro*-2-(3,4-Dibenzyloxyphenyl)butane-2,3-diol** (**15**).—To *erythro*-2-(3,4-dibenzyloxyphenyl)butane-2,3-diol (**15**) (2.00 g, 5.30 mmoles) in 125 ml of anhyd C_6H_6 was added *p*-TsOH (0.030 g). The reaction mixt was refluxed for 12 hr using a Dean–Stark trap to collect the H_2O formed. The C_6H_6 was washed with 5% $NaHCO_3$ soln and H_2O. The C_6H_6 soln was dried ($MgSO_4$) and the solvent was removed to yield a yellowish oil, 1.95 g. The crude ketone was purified by formation of the oxime to yield after recrystn (Et_2O) 1.327 g (66.5%) of **19**: ir (neat) 1710 cm^{-1} (C=O). *Anal.* 2,4-DNP deriv ($C_{30}H_{28}N_4O_6$) C, H, N.

B. **From *threo*-3-(3,4-Dibenzyloxyphenyl)-2-butanol** (**20**).—Compd **20** (0.55 g, 1.45 mmoles) was dissolved in 5 ml of anhyd DMSO and 4 ml of anhyd C_6H_6 containing DCC (0.90 g, 4.35 mmoles). Anhyd *o*-H_3PO_4 (0.010 g, 0.1 mmole) in 0.5 ml of DMSO was added and the reaction mixt was stirred at 25° for 12 hr. Et_2O (50 ml) was added followed by a soln of oxalic acid (0.391 g, 4.35 mmoles) in CH_3OH (5 ml). After gas evoln had ceased, the insol dicyclohexylurea was removed by filtration. The Et_2O layer was washed with 5% $NaHCO_3$ soln and H_2O. The Et_2O fraction was dried ($MgSO_4$) and the solvent was removed to yield 0.52 g of a yellowish oil. The crude ketone was purified by formation of the oxime **21** to yield 0.330 g (61%); mp 118–121°.

3-(3,4-Dibenzyloxyphenyl)-2-butanone Oxime (**21**).—To 3-(3,4-dibenzyloxyphenyl)-2-butanone (**19**) (1.950 g, 5.30 mmoles) in 75 ml of abs EtOH was added $NH_2OH·HCl$ (1.00 g) and NaOAc (1.00 g) in 25 ml of H_2O. The reaction mixt was refluxed for 30 min after which H_2O was added. The resulting crystals were removed by filtration, dried, and recrystd (Et_2O) to yield 1.627 g (82%) of **21**, mp 118–119°. *Anal.* ($C_{24}H_{25}NO_3$) C, H, N.

Reduction of 3-(3,4-Dibenzyloxyphenyl)-2-butanone Oxime (**21**). **A. LAH Reduction.**—To a soln of LAH (0.673 g, 17.7 mmoles) in 50 ml of anhyd THF was added dropwise a soln of oxime **21** (1.327 g, 3.54 mmoles) in 100 ml of anhyd THF. The reaction mixt was allowed to reflux for 16 hr after which "wet" Et_2O followed by H_2O was added to decompose excess LAH. The aq soln was extd several times with Et_2O, and the combined Et_2O fractions were washed with H_2O and satd NaCl soln. The Et_2O soln was dried ($MgSO_4$), and the Et_2O was removed to afford a colorless oil, 1.25 g. Chromatog of the oil on silica gel, eluting with 3% MeOH–$CHCl_3$, afforded 3 major fractions.

Fraction A. *threo*-**2-Amino-3-(3,4-dibenzyloxyphenyl)butane.**—Formation of the HCl salt and recrystn (EtOH–Et_2O) afforded 54 mg (4%) of **22**, mp 161–162°. *Anal.* ($C_{24}H_{28}ClNO_2$) C, H, N.

Fraction B consists of a mixt of *threo*- and *erythro*-2-amino-3-(3,4-dibenzyloxyphenyl)butane.

Fraction C. *erythro*-**2-Amino-3-(3,4-dibenzyloxyphenyl)butane.**—Formation of the HCl salt and recrystn (EtOH–Et_2O) afforded 82 mg (6%) of **23**, mp 132–134°. *Anal.* ($C_{24}H_{28}ClNO_2$) C, H, N.

B. Sodium Bis(2-methoxyethoxy)aluminum Hydride Reduction.[12] To a soln of Na bis(2-methoxyethoxy)aluminum hydride [2.16 g, 3.10 g of a 70% C_6H_6 soln (Aldrich), 9.84 moles] in 10 ml of anhyd C_6H_6 was added dropwise a soln of 3-(3,4-dibenzyloxyphenyl)-2-butanone oxime (**21**) (1.00 g, 2.66 mmoles) in 50 ml of C_6H_6. The reaction mixt was refluxed for 1 hr after which "wet" C_6H_6 followed by H_2O was added to decomp excess hydride. The H_2O layer was extd several times with C_6H_6 and the combined C_6H_6 fractions were washed with H_2O, 5% NaOH soln, and satd NaCl soln. The combined C_6H_6 fractions were dried ($MgSO_4$), and the C_6H_6 was removed to afford a colorless oil, 0.930 g. Chromatog on silica gel, eluting with 2% MeOH–$CHCl_3$, afforded 410 mg of a colorless oil. Formation of the HCl salt and recrystn (EtOH–Et_2O) afforded 0.392 g (38%) of **22**, mp 161–162°.

threo-**2-Amino-3-(3,4-dihydroxyphenyl)butane·HCl** (**4**).—To *threo*-2-amino-3-(3,4-dibenzyloxyphenyl)butane·HCl (**22**) (0.180 g, 0.45 mmole) in 5 ml of anhyd MeOH was added 50 mg of 10% Pd/C under N_2. The reaction mixt was hydrogenated at 25° under atm pressure. The reaction was stopped after consumption of the theor amt of H_2. The catalyst was removed by filtration and the solvent was removed. The resulting oil was crystd (MeOH–Et_2O) to yield 80 mg (82%) of **4**: mp 212–214°; nmr (CD_3OD) δ 6.86–6.68 (m, 3 H, arom), 3.43 (m, 1 H, C-2 C**H**), 2.80 (m, 1 H, C-3 CH), 1.38 (d, 3 H, C-1 C**H**$_3$), 1.28 (d, 3 H, C-1 C**H**$_3$). *Anal.* ($C_{10}H_{16}ClNO_2$) C, H, N.

threo-**3-(3,4-Dibenzyloxyphenyl)-2-butanol 2-Mesylate** (**24**).—To *threo*-3-(3,4-dibenzyloxyphenyl)-2-butanol (**20**) (1.82 g, 5.0 mmoles) in 15 ml of anhyd C_6H_5N, cooled in an ice bath, was added CH_3SO_2Cl (1.26 g, 11.2 mmoles) in 4 ml of anhyd C_6H_5N. The reaction mixt was allowed to remain for 16 hr at 0° after which H_2O was added and the aq layer was extd several times with Et_2O. The combined Et_2O fractions were washed with H_2O and satd NaCl soln and dried ($MgSO_4$), and the solvent was removed to yield a colorless oil which crystd upon standing. Recrystn (Et_2O–hexane) afforded 2.02 g (84%) of **24**, mp 52.5–54°. *Anal.* ($C_{25}H_{28}O_5S$) C, H.

erythro-**2-Amino-3-(3,4-dibenzyloxyphenyl)butane·HCl** (**23**).—To *threo*-3-(3,4-dibenzyloxyphenyl)-2-butanol 2-mesylate (**24**) (1.25 g, 2.84 mmoles) dissolved in 10 ml of DMF was added a soln of NaN_3 (0.92 g, 14.2 mmoles) in 10 ml of H_2O. The reaction mixt was heated at 90–100° for 16 hr, and allowed to cool to 25° after which H_2O was added. The aq layer was extd several times with Et_2O and the combined Et_2O layers were extd with H_2O and satd NaCl soln. The Et_2O fraction was dried

($MgSO_4$), and the solvent was removed to yield 1.28 g of **25**, a yellowish oil, ir (neat) 2110 cm^{-1} (azide). A soln of LAH (0.570, 15.0 mmoles) in 25 ml of anhyd Et_2O was refluxed for 2 hr after which the crude azide **25** in 50 ml of anhyd Et_2O was added at such a rate as to maintain reflux. The reaction mixt was refluxed for 2 hr after which "wet" Et_2O followed by H_2O was added to decomp the excess LAH. The aq layer was extd several times with Et_2O and the combined Et_2O fractions were washed with H_2O and satd NaCl soln and dried ($MgSO_4$), and the solvent was removed to yield a colorless oil, 1.525 g. Chromatog on silica gel, eluting with 5% MeOH-$CHCl_3$, afforded a colorless oil, 0.850 g. Formation of the HCl salt and recrystn (EtOH-Et_2O) afforded 0.567 g (51%) of **23**, mp 132–134°.

erythro-**2-Amino-3-(3,4-dihydroxyphenyl)butane·HCl** (**3**).—To *erythro*-2-amino-3-(3,4-dibenzyloxyphenyl)butane·HCl (**23**) (0.200 g, 0.5 mmole) in 5 ml of anhyd MeOH was added 50 mg of 10% Pd/C under N_2. The reaction mixt was hydrogenated at 25° under 1 atm of H_2. The reaction was stopped after consumption of the theoretical amt of H_2. The catalyst was removed by filtration and the solvent was removed *in vacuo*. The resulting solid was crystd (MeOH-Et_2O) to yield 83 mg (79%) of **3**: mp 254–258°; nmr CD_3OD δ 6.83–6.63 (m, 3 H, arom), 3.39 (m, 3 H, C-2 C**H**), 2.85 (m, 1 H, C-3 C**H**), 1.35 (d, 3 H, C-1 CH_3), 1.15 (d, 3 H, C-4 CH_2). *Anal.* ($C_{10}H_{16}ClNO_2$) C, H, N.

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Acenaphthene Chemistry. 2. Synthesis and Antiinflammatory Activity of 1-[2-(Dimethylamino)ethyl]-2,2-dimethyl-1-acenaphthenecarboxamide[1]

INGEBORG T. HARPER AND SEYMOUR D. LEVINE*

The Squibb Institute for Medical Research, New Brunswick, New Jersey 08903

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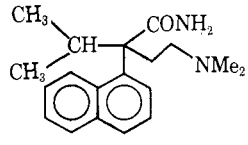
The synthesis and antiinflammatory activity of 1-[2-(dimethylamino)ethyl]-2,2-dimethyl-1-acenaphthenecarboxamide (**2**) are presented. The nature of the products obtained during attempted cyanide displacement reactions on 1-bromo-2,2-dimethylacenaphthene (**14**) under a variety of conditions is described.

The synthesis and antiinflammatory activity of α-isopropyl-α-[2-(dimethylamino)ethyl]-1-naphthylacetamide (**1**) has been reported.[2] If one envisions formation of a bond between the central C atom of the side-chain *i*-Pr group and the C-8 position of the naphthalene ring of **1**, then the acenaphthene **2** is derived. In this paper, we describe the synthesis and antiinflammatory activity of this "bridged" compound, as well as the chemistry of some intermediates.



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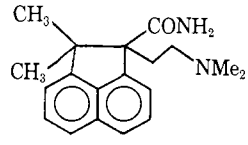
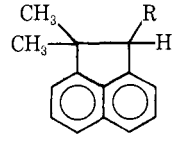
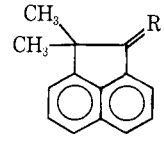


2

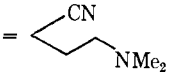
Our successful approach utilized the alcohol **3** as starting material.[3] Sarett[4] or Cornforth oxidation[5] of **3** led to the recovery of **3** as the major product. MnO_2 (active) oxidation[6] of **3** gave a mixture of **3** and the ketone **5**.[3] Oxidation of **3** with Jones reagent[7] gave the carboxylic acid **4**, along with **5**. The ketone may arise from oxidative cleavage of the benzylic C–C bond of **3** or by further oxidation of **4**. The acid was converted into a nitrile (**8**) in the usual manner, and then alkylated with dimethylaminoethyl bromide to give **9**. When **9** was treated under the same drastic acidic conditions employed for the hydrolysis of the corresponding nitrile in the synthesis of **1**,[2] a multicomponent mixture (6 spots, tlc) was obtained in 25% yield. Attempted hydrolysis of **9** with H_2O_2 in NH_4OH was also unsuccessful.[8] While PPA is an excellent reagent for the hydrolysis of unhindered aromatic nitriles, it has been found unsuitable for use with sterically hindered nitriles.[9] Nevertheless, exposure of our hindered nitrile **9** to PPA gave the amide **2** in over 70% yield.



3, R = CH_2OH
4, R = CO_2H
6, R = COCl
7, R = $CONH_2$
8, R = CN



5, R = O

9, R = 

We had originally sought to prepare **8** in a more direct manner by displacement of a suitable acenaphthyl derivative with CN^-. Reduction of **5** with $NaBH_4$ gave the alcohol **10** that was treated with TsCl in pyridine to afford **11**. The formation of such salts from aryl carbinols and allylic hydroxy steroids has been reported recently.[10,11] Treatment of **10** with TsCl in DMF

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