(0.78 mole) of $HCOONH_4$ was treated as described in the preceding paragraph, 43.1 g (73%), recrystd from MeCN–MeOH, mp 293–294°. *Anal.* ($C_{12}H_{12}ClN \cdot HCl$) C, H; N: calcd, 5.79; found, 5.22.

Biological Methods. Blood Collection and Isolation of Plasma. Whole blood was obtained from voluntary, experienced donors before breakfast. Donors were instructed to take no drugs, specifically aspirin, for 5 days before giving blood. If the plasma was lipidemic or, in a preliminary aggregation experiment, showed no second phase aggregation (aspirin-like effect), this plasma was not used. Blood was collected by the 2-syringe technique. It was decalcified with 3.8% sodium citrate soln (1:9 with blood). The citrated bloodwas centrifuged at 100*g* for 10 min and citrated platelet-rich plasma (PRP) was isolated. Platelet-poor plasma (PPP) was isolated by recentrifuging the blood residue at 1500*g* for 15 min.

Inhibition of Platelet Aggregation. Compounds were tested for inhibition of ADP- and collagen-induced aggregation in a Bryston platelet aggregometer by the procedure of Mustard, *et al.*[6] Human platelet-rich plasma (PRP) was diluted with autologous platelet-poor plasma to 400,000 platelets/mm³. Solns of test compd were prepd and added to obtain the indicated concs. Saline was added to another sample of the same plasma to serve as control. After incubation for 20 min at 37°, ADP (2 μg/ml of final concentration) was added to induce aggregation. Platelet aggregation produces an increase in light transmittance (ΔT) through the plasma sample in the aggregometer and this response was recorded on a Bausch and Lomb VOM-5 chart recorder. The maxima of the ΔT responses for control and test sample were then used to calculate per cent inhibition of platelet aggregation by the test compound.

Collagen was prepared by the method of Hovig[25] and was standardized.[9] The values given in Table I refer to inhibition of the initial slope of the aggregation curve, as discussed elsewhere.[10]

Platelet Factor 3 Activation. A soln of the test compd was added to human citrated PRP and incubated at 37° for 20 min, and a modified Stypven test was performed. The plasma was diluted 1:10 for this modified test.[7]

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Treloxinate and Related Hypolipidemic 12*H*-Dibenzo[*d*,*g*][1,3]dioxocin-6-carboxylate Derivatives[1]

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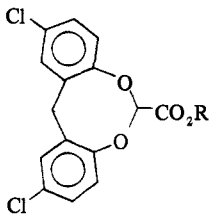
Synthetic studies on *o*-phenylenedioxyacetic acids led to preparation of 2,10-dichloro-12*H*-dibenzo[*d*,*g*]-[1,3]dioxocin-6-carboxylic acid, and its methyl ester, treloxinate, was found to be a potent hypolipidemic agent. Structural modifications of treloxinate and the effect of these on hypocholesterolemic and hypotriglyceridemic activity were explored in rats (Wistar strain). Variation of aromatic substitution patterns and the size of the central heterocyclic ring resulted in decrease or loss of activity. A general synthetic method was developed to prepare analogous tricyclic acids from bisphenols and excess potassium dichloroacetate in hydroxylic solvents. Yields were affected by the size of the central ring and by aromatic substitution but surprisingly little by steric hindrance.

A large number of alkylcarboxylic acids with aryl or aryloxy substituents have been reported to have hypolipidemic activity.[2] Clofibrate, ethyl 2-(*p*-chlorophenoxy)-2-methylpropionate, is one of the more effective of these agents, and is the most widely used for control of hyperlipidemias associated with atherosclerotic cardiovascular diseases. This

compound, in addition to reducing plasma or serum cholesterol, also reduces circulating triglycerides. One of its disadvantages is its low potency, 1-2 g per day being required for effective therapy.[3] Also, its effectiveness varies in regard to the types of hyperlipoproteinemias, as defined by the Fredrickson classification,[4] and in particular, clofibrate has been shown in several studies to be less effective in type II hyperlipoproteinemia.[5] This explains the continued search by us and many other research groups for superior hypolipidemic agents.

2,10-Dichloro-12*H*-dibenzo[*d*,*g*] [1,3] dioxocin-6-carboxylic acid (**1**) was first prepared as an extension of synthetic studies on *o*-phenylenedioxyacetic acids.[6] In rats of the Sprague-Dawley strain,† compound **1** was found to affect serum triglycerides, but not cholesterol. Reevaluation in rats of the Wistar strain,‡ however, showed **1** to have general hypolipidemic activity. This carboxylic acid (**1**) is about 8 times more potent in lowering serum cholesterol and 30 times more potent in lowering serum triglycerides, compared to clofibrate. Its mechanism of action differs from that of clofibrate in several respects.[7] Its methyl ester **2** has been named treloxinate[8] and is currently undergoing clinical trial. The ester is rapidly hydrolyzed after absorption to the free carboxylic acid.[9] The activities of treloxinate (**2**) and its acid form (**1**) have been found to be identical.



1, R = H
2, R = CH_3

It is apparent from its structure that treloxinate contains structural elements of clofibrate. It is even more closely related to 1-methyl-4-piperidyl 2,2-bis(*p*-chlorophenoxy)acetate (**24**),§ and may be viewed as a cyclic analog of it. The methylene bridge formed by the C-12 atom of the dibenzo[*d*,*g*] [1,3] dioxocin system confers structural rigidity on the molecule as a whole, as can be seen in molecular models and ir and nmr spectra.

Structure-Activity Relationships. We explored a number of structural modifications of treloxinate. These are listed in Table I. The compounds were evaluated in rats of the Wistar strain‡ and were administered for 10 days by admixture to the diet. The daily dose was calculated from food consumption. The degree of reduction of plasma cholesterol and triglycerides that resulted is recorded in the last two columns of Table I. The esters **2-8** generally showed the same degree of hypolipidemic activity as the parent free acid **1**. This is due to their metabolic conversion to the free acid, a conversion that has been shown to occur for treloxinate itself.[9] Aromatic substitution patterns were explored by preparation of compounds **9-16**. Congener **12** without chlorine substitution at positions 2 and 10 was much less active than treloxinate. Witiak, *et al.*,[12] found the corresponding modification of clofibrate to result in little loss of activity. Replacement of the chlorine substituent by methyl groups, **14**, resulted in loss of activity in both instances.[12] The dichlorodimethyl congener **13**, the di-*tert*-butyldimethyl congener **15** and the tetrachloro congeners **9** and **10** were inactive while the hexachloro congener **11** and compound **16**, with fused benzo rings at the 1,2 and 10,11 positions, had significant activity. When the methylene bridge (C-12) of treloxinate was replaced by a bond to give the dibenzo[*d*,*g*] [1,3] dioxepin-6-carboxylic acids and esters **17-20**, little or no hypocholesterolemic activity was found but some hypotriglyceridemic activity remained.

Finally, the dicarboxylate **21** and compound **22** in which the carboxylate function was reduced to a hydroxymethyl group were inactive. Similarly **25**, in which the carboxylate function of **23** was reduced, was inactive. The compound corresponding to clofibrate, **26**, also did not significantly lower serum lipids.[11]

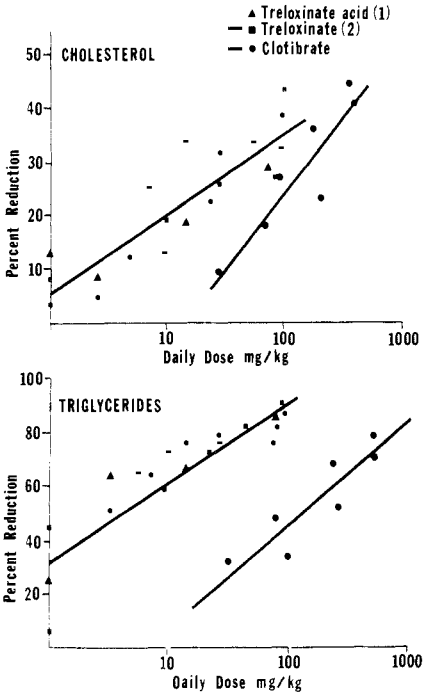
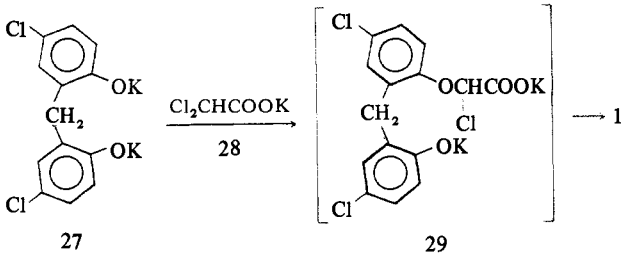


Figure 1. Dose-resposne curves for the hypolipidemic effect of treloxinate acid (1), treloxinate (2), and clofibrate in immature Wistar rats on oral medication for 10 days.

Serum cholesterol and triglyceride dose-response curves for treloxinate **2** and its acid **1** are given in Figure 1 along with those of clofibrate.

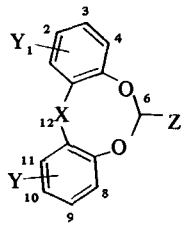


27 29

Chemistry. 2,10-Dichloro-12*H*-dibenzo[*d*,*g*] [1,3] dioxocin-6-carboxylic acid (**1**) was prepared from 2,2'-methylenebis(4-chlorophenol) (**27**) and potassium dichloroacetate (**28**). This seemingly simple reaction that initially gave very low yields proved to be more difficult to improve than anticipated. After about 100 trials, a procedure was developed that consistently gave 80-85% yield. These studies are summarized in Table II. We found that (a) potassium dichloroacetate was a much more effective reagent than the corresponding ester, methyl dichloroacetate, (b) that a hydro-

†Charles River Breeding Laboratories, Inc., Wilmington, Mass.
‡Royalhart Laboratory Animals, Inc., New Hampton, N. Y.
§SaH 42-348, generously supplied by Sandoz Pharmaceuticals.

Table I. 12*H*-Dibenzo[*d*,*g*][1,3]dioxocin-6-carboxylate Derivatives. Hypolipidemic Activity



No.	X	Y 1,11	Y 2,10	Y 4,8	Z	Mp, °C[a]	Recrystn solvent[b]	Formula	Analysis[c]	Yield[d] of cycliza-tion, %	Plasma lipids, rats[e] Dose,[f] mg/kg	% reduction *vs.* control Choles-terol	% reduction *vs.* control Triglyc-erides
1	CH_2	H	Cl	H	COOH	246-250 d	A	$C_{15}H_{10}Cl_2O_4$	C, H	85	28	32[g]	79[g]
2	CH_2	H	Cl	H	$COOCH_3$	216-218	B	$C_{16}H_{12}Cl_2O_4$	C, H, Cl		25	23[g]	71[g]
3	CH_2	H	Cl	H	$COOC_2H_5$	167-168	C	$C_{17}H_{14}Cl_2O_4$	C, H, Cl		29	28[g]	76[g]
4	CH_2	H	Cl	H	$COOCH(CH_3)_2$	131-133	D	$C_{18}H_{16}Cl_2O_4$	C, H, Cl		25	18[g]	63[g]
5	CH_2	H	Cl	H	$COO(CH_2)_3OCO$[i]	169-172	E	$C_{33}H_{24}Cl_4O_8$	C, H, Cl		30	23[g]	36[g]
6	CH_2	H	Cl	H	COO-(N-CH_3)	184-186	F	$C_{21}H_{21}Cl_2NO_4$	C, H, Cl		30	26[g]	71[g]
7	CH_2	H	Cl	H	$COOCH_2$-(N)	138-142	G	$C_{21}H_{15}Cl_2NO_4$	C, H, N		30	25[g]	70[g]
8	CH_2	H	Cl	H	$COOCH_2CH_2NHAc$	188-190	E	$C_{19}H_{17}Cl_2NO_5$	C, H, N		30	34[g]	80[g]
9	CH_2	H	Cl	Cl	COOH	258-260 d	H	$C_{15}H_8Cl_4O_4$	C, H, Cl	82	31	1[h]	17[h]
10	CH_2	H	Cl	Cl	$COOCH_3$	184-186	I	$C_{16}H_{10}Cl_4O_4$	C, H, Cl		31	2[h]	5[h]
11	CH_2	Cl	Cl	Cl	$COOC_2H_5$	172-175	C	$C_{17}H_{10}Cl_6O_4$	C, H[j]	*k*	56	25[g]	43[g]
12	CH_2	H	H	H	$COOCH_3$	108-109	B	$C_{16}H_{14}O_4$	C, H	*k*	30	9[h]	13[h]
											211	6[h]	44[g]
13	CH_2	H	Cl	CH_3	$COOCH_3$	267-271d	E	$C_{18}H_{16}Cl_2O_4$	C, H, Cl	76	30	0	27
14	CH_2	H	CH_3	H	$COOCH_3$	158-160	I	$C_{18}H_{18}O_4$	C, H	35	26	13[h]	36[h]
											147	16[h]	62[g]
15	CH_2	H	CH_3	$C(CH_3)_3$	$COOCH_3$	210-215	I	$C_{26}H_{34}O_4$	C, H	13	25	7[h]	38[h]
16	CH_2			H	$COOCH_3$	176-178	I	$C_{24}H_{18}O_4$	C, H	45	32	16[g]	58[g]
17[l]	Bond	H	H	H	COOH	111-113	K	$C_{14}H_{10}O_4$	C, H	*k*	64	5[h]	2[h]
18	Bond	H	Cl	H	$COOCH_3$	102-104	I	$C_{15}H_{10}Cl_2O_4$	C, H, Cl	14[m]	30	6[h]	53[g]
19	Bond	H	Cl	Cl	COOH	235-238	H	$C_{14}H_6Cl_4O_4$	C, H, Cl	57[m]	32	7[h]	38[g]
20	Bond	H	Cl	Cl	$COOCH_3$	148-150	I	$C_{15}H_8Cl_4O_4$	C, H, Cl		45	15[g]	64[g]
21	CH_2	H	Cl	H	$CH(COOC_2H_5)_2$	117-118	J	$C_{20}H_{18}Cl_2O_6$	C, H, Cl	*k*, *n*	153	0	0
22[o]	CH_2	H	Cl	H	CH_2OH	128-130	1	$C_{15}H_{12}Cl_2O_3$	C, H[p]		29	6[h]	19[h]
											272	4[h]	0
23	H, H	H	Cl	H	COOH						31	40[g]	65[g]
24[q]	H, H	H	Cl	H	COO-(N-CH_3)						24	28[g]	70[g]

25[o]	H, H	H	Cl	H	CH_2OH	59–61	K	$C_{14}H_{12}Cl_2O_3$	C, H, Cl		196	0	0	
Clofibrate											29	9[h]	32[h]	
											274	38[g]	53[g]	
26[r]											227[s]	20[h]	31[h]	

[a]Melting points are corrected and were taken on a Hoover capillary melting point apparatus. Decomposition points are indicated by d. [b]A = AcOH, B = MeOH, C = Et_2O, D = *i*-PrOH, E = PhMe, F = Me_2CO, G = MeCN, H = Me_2CO–PhMe, I = Me_2CO–MeOH, J = Et_2O–C_6H_{14}, K = C_6H_{14}. [c]Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. [d]Yields indicated refer to those obtained under conditions found optimal or near optimal for the preparation of **1** as described in the Experimental Section. Yields refer to the cyclization step only, *i.e.*, to the free acids. [e]Young male rats of the Wistar strain obtained from Royalhart Laboratory Animals, Inc., New Hampton, N. Y., of average initial weight of 170–190 g, treated in groups of 6 animals for 10 days and compared to an untreated control group. Plasma cholesterol and triglycerides were determined by automated procedures as described in the Experimental Section. [f]Daily dose administered by admixture to food at levels of 0.03 and 0.25%. Actual dose calculated from food consumption. [g]Statistically significant values at $p > 0.05$. [h]Nonsignificant values at $p > 0.05$. [i]Bis ester. [j]Cl: calcd, 43.32; found, 42.80. [k]Obtained in low yield. Prepared before optimum conditions for cyclization were learned. [l]The ethyl ester was reported by Breslow and Mohacsi.[10] [m]See Experimental Section for special reaction conditions. [n]From diethyl dibromomalonate. [o]Obtained by $LiAlH_4$ reduction of 2 or 23, respectively, in THF. [p]Cl: calcd, 22.79; found, 22.30. [q]See footnote g. [r]See ref 11. [s]In Sprague–Dawley rats, in which clofibrate is effective at 250–300 mg/kg per day, this compound did not reduce serum cholesterol or triglycerides at 315 mg/kg per day for 10 days.

xylic solvent and a reaction time of 3–5 days was required, and (c) that an excess of potassium dichloroacetate, preferably added in part after the first 24 hr of reaction time, markedly improved the yield. The last finding was surprising and indicated that competing inter- and intramolecular reactions in the ring closure of **29** are not a critical factor. Generally, potassium carbonate was used as the base except for the preparation of the dibenzo[*d*,*g*][1,3]dioxepins **18** and **19** that required a stronger base, such as sodium methoxide.

The successful application of these optimum conditions for ring closure to obtain the congeners listed in Table I indicates that the reaction is general. It is interesting to compare the yields given in column 11. It can be seen that the formation of the 7-membered ring of the dibenzodioxepins **18** and **19** is more difficult than that of the 8-membered rings of dibenzodioxocins (**1**, **9**). While the inductive effect of aromatic substituents appears to play a role (**14** *vs.* **1**; **18** *vs.* **19**), steric hindrance appears to have little effect. Chlorine or methyl substitution in the ortho position of the phenolic groups involved in the ring closure did not diminish the yield of **9**, **13**, and **19**, and even the presence of large *tert*-butyl groups (to give **15**) is permissible. Dreiding molecular models also indicate possible steric interaction of the hydrogen atoms in positions 1 and 15 of the dinaphtho congener **16** but cyclization occurred in reasonable yield.

The unsubstituted congener **12** was obtained by cyclization of the corresponding bisphenol but could also be obtained by dehalogenation of the sodium salt of **1**, using hydrazine hydrate in refluxing ethanol over Pd/C catalyst,[13] followed by esterification. Of interest also is the preparation of 2,2′-methylenedi-*p*-cresol required for preparation of **14**. It was obtained by de-*tert*-butylation of 2,2′-methylenebis(6-*tert*-butyl-*p*-cresol) under Friedel-Crafts reaction conditions,[14] as described in the Experimental Section. Most of the remaining bisphenols were obtained from commercial sources# and their preparation is described in the literature.[15-17] The esters were prepared using conventional methods.

Spectral Data. Several features of the nmr, uv, and ir spectra of treloxinate (**2**) and its congeners reflect the structural rigidity of this ring system. Pertinent data are given in Table III. The nmr spectra of the 12*H*-dibenzo[*d*,*g*][1,3]dioxocins show the C-12 protons to be nonequivalent because of a specific cis-trans stereochemical relationship to the functions on the 6 position. The corresponding symmetrical compound **21** has equivalent C-12 protons. Comparison of the C-6 protons in cyclic compounds **1** and **6** with the corresponding α protons in the noncyclic analogs (**23** and **24**, respectively) shows a 0.9–1.25 ppm upfield chemical shift in the cyclic molecules. In addition, the intensity (ϵ) of uv absorption in the 270- to 280-nm region is markedly diminished in the cyclic structures, and the ir carbonyl absorption is shifted 20 cm^{-1} higher in the corresponding cyclic molecules. In the 12*H*-dibenzo[*d*,*g*][1,3]dioxocin system, neither the oxygen p orbitals nor the aromatic π cloud is free for unrestricted interaction with the C-6 proton. Likewise, the uv intensity is lower because of diminished overlap of the p orbitals of the oxygen atoms with the aromatic π cloud. Indeed, Dreiding molecular models indicate that it is difficult for the p orbitals to line up parallel with the aromatic π cloud. The same nmr and uv relationships as described above can

#Samples of several bisphenols were generously supplied by the Givaudan Corp.

Table II. Yield of 1 with Variation of Reaction Conditions[a]

Solvent	$Cl_2CHCO_2CH_3$ 1 equiv	$Cl_2CHCO_2CH_3$ 2 equiv	Cl_2CHCO_2H 1 equiv	Cl_2CHCO_2H 2 equiv, 2nd equiv added after 10 hr	Cl_2CHCO_2H 2 equiv, 2nd equiv added after 24 hr
H_2O			5	31	
MeOH	0				
MeOH[b]	12		33		
EtOH	23				
i-PrOH	37	37	42	64	86
n-PrOH				64	
n-BuOH	39				
tert-BuOH	8			54	
DMF				31	
2-Pyrolidinone	10				
Dioxane	<5				
Toluene	<5				
DMSO	10				

[a]See Experimental Section for description of general procedure. [b]The reaction mixture was refluxed for 7 days.

Table III. Spectral Data

Compd	Nmr,[a] δ, ppm H_{12a}	H_{12b}	H_6	$J_{12a-12b}$	Uv[b] λ_{max}, nm (ε)	ir,[c] cm^{-1}
14	3.35	4.59	5.08	13	277 (1.897)	1770
12	3.46	4.60	5.09	13	265 (1,193)	1770
2	3.40	4.53	5.05	13	281 (1,830)	1765
6	3.40	4.50	5.03	13	281 (1,050)	1760
10	3.46	4.67	5.08	13	276 (1,170)	1775
22	3.62	4.27	4.62[d]	13	281 (2,080)	
1	3.75	4.40	5.20[d]	13	280 (720)	1730
11	4.45	4.75	5.69	15		1765
16	4.69	5.19	5.85	16	280 (10,450)	1765
21	4.08				271 (1,160)	1760
25			5.72		278 (2,260)	
18			5.92		285 (3,800)	1765
24			5.93		277 (1,980)	1740
23			6.45[d]		276 (1,980)	1710

[a]In $CDCl_3$ unless otherwise indicated. [b]In MeOH. [c]In KBr. [d]In DMSO-d_6.

be seen in the cyclic and noncyclic alcohols (22 and 25, respectively). The mass spectrum (70 eV) of treloxinate (2) showed *m/e* (rel intensity) 340 (26), 338 (33), 281 (22), 280 (12), 279 (22), 278 (26), 251 (36), 249 (66), 217 (18), 215 (62), 188 (10), 186 (28), 181 (33), 152 (100), 140 (53), 93 (28), 77 (29), 76 (36), 75 (51), 63 (38), 59 (22), and 51 (33).

Experimental Section**

Biological Methods. Young male rats of the Wistar strain, obtained from Royalhart Laboratory Animals, Inc., New Hampton, N. Y., of average initial weight of 170–190 g were used in these tests. The compounds to be tested were mixed thoroughly with Purina Lab Chow (Ralston Purina Co., St. Louis, Mo.), and the diet was fed *ad libitum* to groups of 6 animals for 10 days. An untreated control group was included in each experiment. Food consumption was determined by weighing the feeders, and these data were used to calculate the average daily dose of the test compounds. At the end of the 10-day treatment period, the rats were bled by cardiac puncture. Plasma cholesterol[18] and triglyceride[19] levels were determined by automated procedures.

Values for plasma cholesterol and triglyceride concentration in the treated animals were compared with the values obtained for untreated control rats run simultaneously. Significance of the difference between the values was calculted by the *t* test. The data are expressed as per cent reduction from control levels.

Using these methods, cholesterol and triglyceride concentration in plasma of control rats averaged 68 and 91 mg/100 ml, respectively.

**See footnotes *a* and *c*, Table I.

2,10-Dichloro-12*H*-dibenzo[*d,g*][1,3]dioxocin-6-carboxylic Acid (1), Derivatives and Analogs. General Cyclization Procedure. A mixt of 100 g (0.372 mole) of 2,2′-methylenebis(4-chlorophenol), 206 g (1.488 mole) of K_2CO_3, 15.5 g (0.073 mole) of KI, 48.0 g (0.372 mole) of Cl_2CHCO_2H, and 1.5 l. of *i*-PrOH was refluxed with vigorous stirring for 30 hr. The mixt was cooled and an addnl 48.0 g (0.372 mole) of Cl_2CHCO_2H was added. The reaction was refluxed with stirring for an addnl 60 hr, then the *i*-PrOH was distd off and replaced with H_2O. The mixt was cooled, and the ppt collected and washed with 0.3 *N* KOH. The moist solid was suspended in 3 l. of H_2O, 2 *N* HCl was added until the mixt was strongly acidic, and stirring was continued for 2 hr. The ppt was collected, washed with H_2O, and dried, affording 104.5 g (86%), mp 225–235° dec. Recrystn from HOAc gave 102.0 g (85%) of 1, mp 242-244° dec.

Slight modification of this procedure included the omission of KI, which resulted in 82% yield of 1, and the use of $NaOCH_3$ as base for compounds 18 and 19. See Table II for variations of reaction conditions. In addition to HOAc, toluene and mixtures of toluene and hexane were used to recryst the acids.

The Na salt of 1 was prepared and recrystd from H_2O to give the dihydrate, mp 340–350° dec. *Anal.* ($C_{15}H_9Cl_2O_4Na \cdot 2H_2O$) C, H, Cl. Its solubility in water was found to be about 1:300.

The acid chloride of 1 was prepared with $SOCl_2$, recrystd from C_6H_6–C_6H_{14}, mp 175–178°. *Anal.* ($C_{15}H_9Cl_3O_3$) C, H, Cl.

The ester 2 was prepared using refluxing MeOH in the presence of a small amount of H_2SO_4, while compds 5–8 were prepared from the acid chloride and the corresponding alcohol in the presence of Et_3N in C_6H_6. One of these two procedures is also recommended for preparation of the esters 3, 4, and 11 that were obtained inadvertently.

Methyl 12*H*-Dibenzo[*d,g*][1,3]dioxocin-6-carboxylate (12). Carboxylic acid 1 (101.5 g, 0.312 mole), KOH (52.0 g, 0.930 mole), and 2.2 l. of EtOH were stirred at room temp for 30 min, Pd/C (1.0 g, 10%) was added, then $NH_2NH_2 \cdot H_2O$ (250 ml, 85% soln) was slowly added, and the mixt was refluxed for 2 hr; $NH_2NH_2 \cdot H_2O$ (250 ml, 85% soln) was again added, and the mixt was refluxed with stirring for 18 hr. The mixt was filtered, and the filtrate was evapd to dryness under reduced pressure. The oil was treated with excess 2 *N* HCl, extd into C_6H_6, washed (H_2O), and dried (Na_2SO_4), and the solvent was evapd under reduced pressure. The resulting crude carboxylic acid (90.0 g, 100% yield) was esterified (MeOH–H_2SO_4) and recrystn from MeOH gave 61.5 g (73%) of 12, mp 100–102°.

2,2′-Methylenedi-*p*-cresol. 2,2′-Methylenebis(6-*tert*-butyl-*p*-cresol) (100 g, 0.294 mole), $AlCl_3$ (100 g, 0.750 mole), and 500 ml of dry C_6H_6 were refluxed for 24 hr. The mixt was poured into HCl–ice. The C_6H_6 layer was washed (H_2O) and extd into 1 *N* KOH. The aqueous ext was acidified, and the resulting ppt was collected, washed (H_2O), and dried, affording 55.0 g (82%) of a tan solid. Recrystn from toluene gave 40.0 g (60%) of the title compd, mp 120–125°, lit.[20] mp 125°. The product was found to be identical with an authentic sample.#

4,4′-Dichloro-2,2′-diphenol. *o,o*′-Biphenol (50 g, 0.269 mole), SO_2Cl_2 (74.5 g 0.55 mole), and 500 ml of $CHCl_3$ were refluxed for 16 hr. The $CHCl_3$ was distd off under reduced pressure. Recrystn from C_6H_6–C_6H_{14} gave 55.0 g (81%) of 4,4′-dichloro-2,2′-diphenol, mp 143–144°, lit.[17] mp 140°.

4,4',6,6'-Tetrachloro-2,2'-diphenol. *o,o'*-Biphenol (50 g, 0.269 mole), SO_2Cl_2 (302 g, 2.24 mole), and 200 ml of C_6H_6 were refluxed for 16 hr. The C_6H_6 was distd off. Recrystn from C_6H_6–C_6H_{14} gave 75.0 g (86%) of 4,4',6,6'-tetrachloro-2,2'-diphenol, mp 166–172°, lit.[21] mp 178°.

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Analgetic 1-Oxidized-2,6-methano-3-benzazocines

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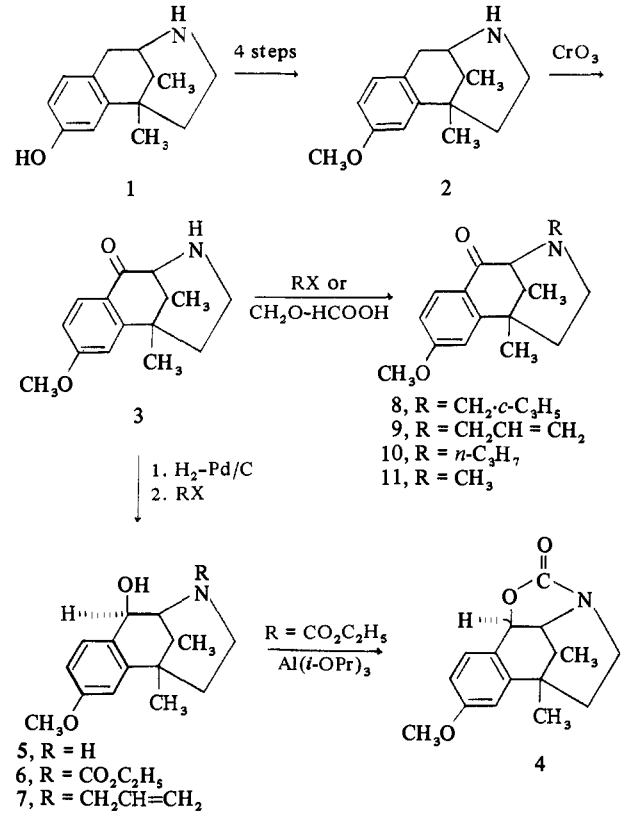
Direct introduction of oxygen on the benzylic carbon of 8-methoxy-2,6-methano-3-benzazocines is described. *N*-Alkyl derivatives have been prepared and one compound, 3-cyclopropylmethyl-3,4,5,6-tetrahydro-8-hydroxy-6(e),11(a)-dimethyl-2,6-methano-3-benzazocin-1(2*H*)-one, has been found to have a noteworthy profile with respect to narcotic antagonist and agonist activities.

In the course of our work on the 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-8-ols, it became desirable to modify the parent ring system by introduction of an oxygen function at position one. A search of the literature revealed that some examples of benzylic position oxidized morphine-like structures existed.[1] None of the authors reported any biological data on these compounds.† Since it is well documented that introduction of a hydroxyl group para to the phenethylamine moiety in morphine-like structures generally enhances analgetic activity, and, further, since we could find only one example[1b] of a related compound bearing both a phenolic hydroxyl and an oxidized benzylic functionality, we prepared a series of such derivatives of 1,2,3,4,5,6-hexahydro-6(e),11(a)‡-dimethyl-2,6-methano-3-benzazocine for evaluation as potential analgetic agents.

Chemistry. The introduction of oxygen at the benzylic position of the compounds referred to above had been achieved in three ways: (1) intramolecular acylation;[1a] (2) photooxidation;[1c] (3) CrO_3 oxidation.[1b] Of these, the first was rejected because it was felt that the synthesis would be too extensive, and the second was rejected because of probable poor yield. This left the third choice, and a suitable substrate for the oxidation was determined in part by literature precedent and in part by our synthetic objectives. Rapoport and Masamune[1b] reported that whereas dihydrodesoxycodeine could be oxidized by CrO_3 in aqueous sulfuric acid, heroin could not be, and since we wished to prepare a series of *N*-alkyl derivatives, the logical starting material was 1,2,3,4,5,6-hexahydro-8-methoxy-6(e),-

Scheme 1



†A recent report by Ziering, *et al.*,[2] which prompted us to report our work, gives data on one such compound.

‡a stands for axial and e for equatorial. Configurations are with respect to the hydroaromatic ring. This nomenclature was adopted in this laboratory when the cis-trans nomenclature became unwieldy for some 2,6-methano-3-benzazocines.