Novel Polycyclic Heterocycles. IX. Dibenz[*b*,*f*][1,4]oxazocin-11(12*H*)one, 6,11-Dihydro-12*H*-dibenz[*b*,*f*][1,4]oxazocine, and their Derivatives (1)

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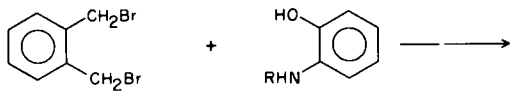
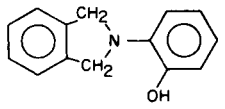
Dibenz[*b*,*f*][1,4]oxazocin-11(12*H*)one, **14**, was synthesized by the dicyclohexylcarbodiimide induced cyclization of α-(*o*-aminophenoxy)-*o*-toluic acid (**13**). Reduction of **14** by lithium aluminum hydride gave 6,11-dihydro-12*H*-dibenz[*b*,*f*][1,4]oxazocine (**16**). Both **14** and **16** were converted to a series of 12-alkylated and -acylated derivatives. The pmr spectra of some of these compounds are discussed.

The preceding paper (3) described the synthesis of several 6,11-dihydro-12*H*-dibenzo[*b*,*f*][1,4]thiazocines. The preparative route involved the reaction of α,α′-dibromo-*o*-xylene (**1**) and an *o*-aminobenzenethiol in dimethylformamide. The corresponding reaction, namely that of **1** and either **2** or its *N*-formyl derivative (**3**) did not yield the oxazocine, but, instead gave **4**. The failure of this one-step procedure required the development of an alternative route but that was found only after a number of others were investigated and found to



1 2, R = H 3, R = HC(=O)



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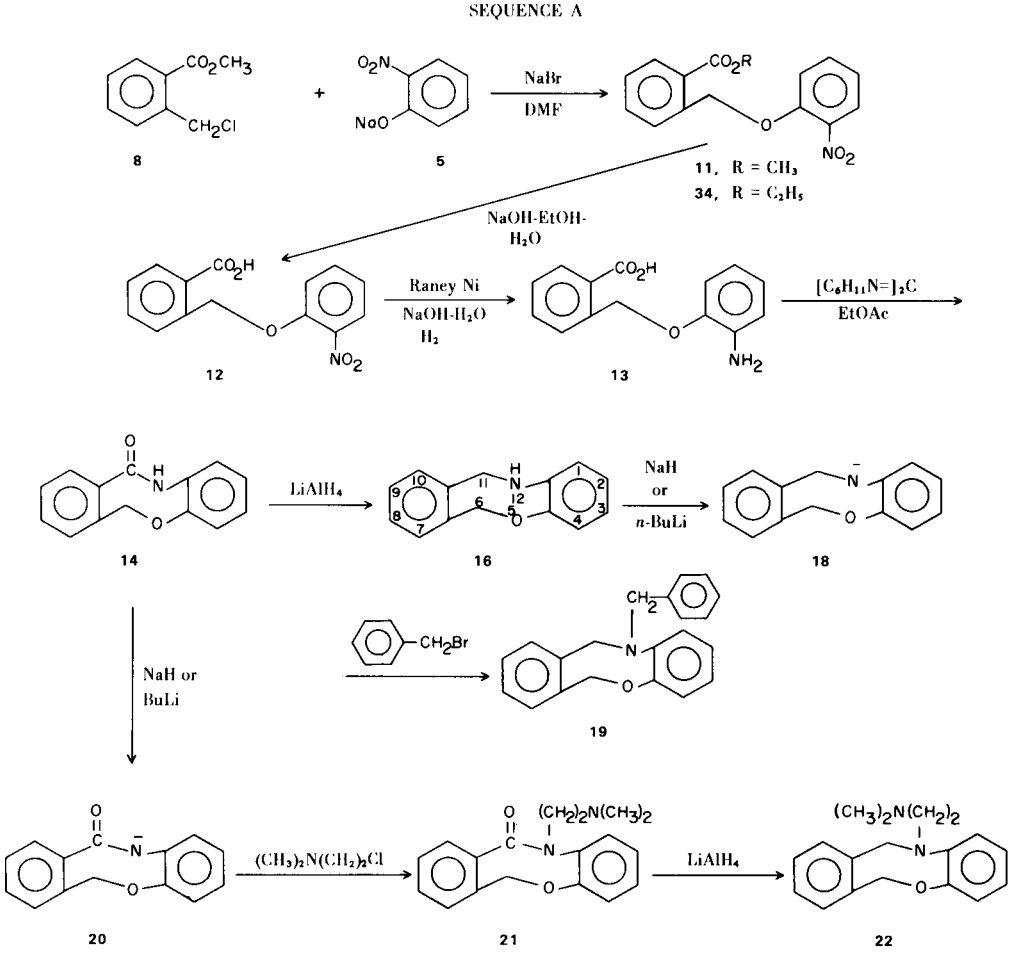
yield aberrant products. For example, **1** and sodium *o*-nitrophenoxide (**5**) in ethanol-dimethylformamide gave α,α′-bis(*o*-nitrophenoxy)-*o*-xylene (**6**); α-bromo-*o*-toluic acid (**7**) and **5** in acetonitrile gave phthalide; methyl α-chloro-*o*-toluate (**8**) and *o*-hydroxyacetanilide in ethanolic sodium methoxide gave methyl α-(*o*-acetamidophenoxy)-*o*-toluate (**9**), but saponification of **9** gave only α-(*o*-acetamidophenoxy)-*o*-toluic acid (**10**) and more severe conditions led only to degradation without yielding the deacetylated derivative.

The sequence of reactions that led to the successful synthesis of 6,11-dihydro-12*H*-dibenz[*b*,*f*][1,4]oxazocine (**16**) is summarized in Sequence A. Incidental to the development of this procedure, several practical problems were uncovered. One of these involved the catalytic hydrogenation of the ethyl ester (**34**). Unexpectedly, hydrogen uptake was slow, not reproducible, and was invariably accompanied by degradation to complex by-products. In contrast, a solution of the carboxylic acid (**12**) in one equivalent of aqueous sodium hydroxide was rapidly hydrogenated to **13** in excellent, reproducible yield. A second problem was encountered in the failure of conventional procedures to convert **13** to **14** (6). This intramolecular cyclization was achieved with dicyclohexylcarbodiimide (DCC) in ethyl acetate (7); while successful, the reaction also yielded significant amounts of the adduct of **13** to DCC (**15**) and **13** could not be recovered from **15** by any known chemical procedure. Lithium aluminum hydride readily converted **14** to **16**. It was significant that **16** reacted with formic acid to give the *N*-formyl derivative (**17**); the homologous 5,11-dihydrodibenz[*b*,*e*][1,4]oxazepines could not be formylated by that reagent (8).

Either **14** or **16** reacted with sodium hydride or *n*-butyllithium to generate the anions, **20**, or **18**, respectively. While **18** was alkylated, in one instance, with benzyl bromide and gave 12-benzyl-6,11-dihydro-12*H*-dibenz[*b*,*f*][1,4]oxazocine, **19**, in 33% yield (9), the usual route involved the alkylation of **20** to give derivatives related to **21**; the latter, of particular interest because of their pmr spectra (see below), were then reduced with lithium aluminum hydride to give the 12-alkylated oxazocines (**22**).

While the anion (**18**) could readily be acylated to give **23**, most of the acyl derivatives, as shown in Sequence B, were prepared by the reaction of **16** with the acyl chloride in toluene-triethylamine. The isolation of a crystalline carbamoyl chloride (**24**) is, in contrast, again, with the behavior of the homologous dibenzoxazepine heterocycles, where the corresponding carbamoyl chlorides have never

SEQUENCE A



been isolated (10). It is of interest that **24** did not react with **16** in toluene-triethylamine, but did react with the anion (**18**) to give the *bis*-compound (**25**).

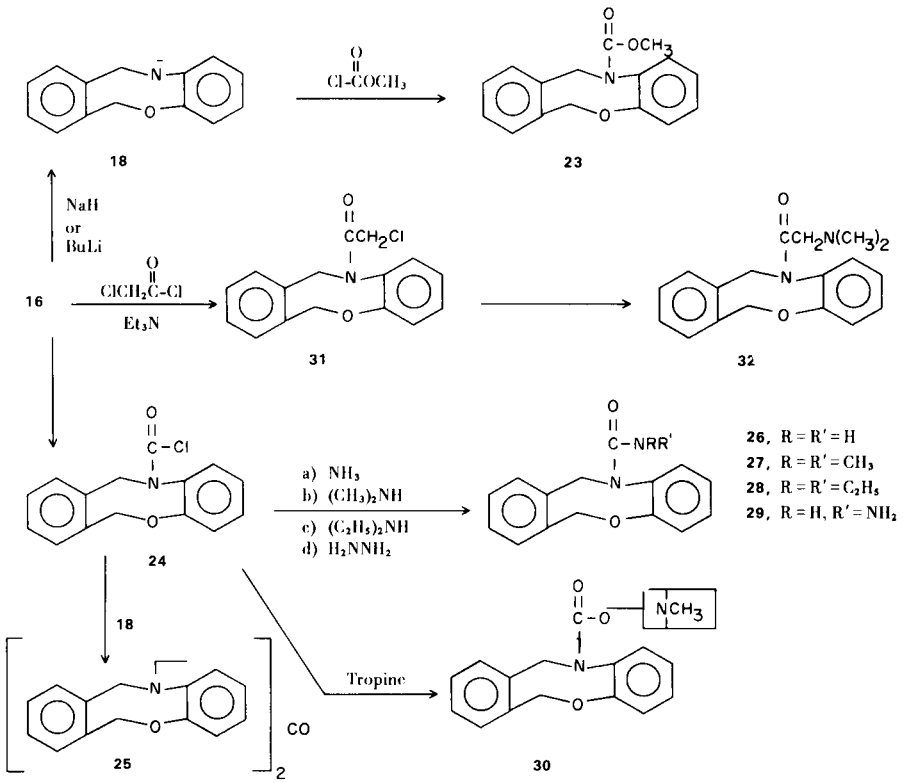
Proton Magnetic Resonance Spectra.

The pmr spectrum of 6,11-dihydro-12*H*-dibenz[*b*,*f*]-[1,4]oxazocine (**16**) showed each methylene group at positions-6 and -11 as a two proton singlet at δ 5.33 and 4.58, respectively. In the *12-benzyl derivative*, three methylene singlets were seen at δ 5.22, 4.50 and 4.43; the first could be assigned unambiguously to position-6, the remaining two were attributed to the two methylene groups attached to nitrogen at position -12. The introduction of carbonyl groups at position-11 in **14**, or at position-12 in **17**, produced the anticipated shifts of the 6-methylene singlet signals to δ 5.51 and 4.98, respectively; in addition, with **17**, the methylene at position-11 was shifted upfield and was seen as a two-proton singlet at δ 5.24. Alkylation of **14** in position-12, as in **21**, converted the singlet at δ 5.51 into an A_2B_2 quartet at δ 5.83 and 4.95, but when the carbonyl group in **21** was reduced, as in **22**, the signals associated with the 6- and 11-methylene groups were again seen as singlets at δ 5.22 and 4.48. Substitution at position-12 by -COCl (**24**), $-CONH_2$ (**26**), $-CON(CH_3)_2$ (**27**), $-CON(C_2H_5)_2$ (**28**), $-CONHNH_2$ (**29**), and $-CO_2CH_3$ (**23**), again deshielded the protons at position-11 and moved those signals downfield while the signals for the methylene protons at position-6 were shifted slightly upfield. In general, the deshielding and shielding of the methylene protons at positions-6 and -11 in the dibenzoxazocines was found to be less pronounced than in the corresponding dibenzothiazocines (3).

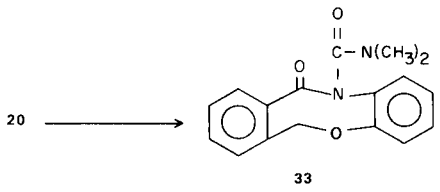
EXPERIMENTAL

The ir spectra were obtained on mineral oil mulls or on deuteriochloroform solutions, employing a Perkin-Elmer 621 spectrophotometer. The pmr spectra were obtained on a Varian A-60. The authors are indebted to Mrs. Barbara Toeplitz and Dr. M. Puar for these spectra. The microanalyses were carried out by Mr. Joseph Alicino and his associates of this Institute. The melting points were determined in capillary tubes in an electrically heated oil bath and are not corrected.

SEQUENCE B



Finally, the anion (**20**) reacted with dimethylcarbamoyl chloride to give **33**.



Methyl α-(*o*-Nitrophenoxy)-*o*-toluate (**11**).

To 103.0 g. (1.0 mole) of sodium bromide and 161.0 g. (1.0 mole) of sodium *o*-nitrophenoxide (**5**) in 1100 ml. of DMF was added, at 20° and in 10 minutes, 186.0 g. (1.0 mole) of methyl α-chloro-*o*-toluate (11). The initial *p*H was 9.0 and this changed to 7.5 after 3 hours of heating at 85-90°. The mixture was cooled, filtered and the filtrate poured into 18 liters of water with vigorous agitation. The solid that separated was filtered and dried to give 223.0 g. of crude **11**; recrystallization from Skellysolve E gave 147.0 g. (50% yield) of **11**, m.p. 109-111°; ν (mull) 1720 (s), 1613 (s), 1583 (s), 1515 (s), 1487 (s), 1442 (s), 1377 (s) cm^{-1}; pmr (deuteriochloroform) δ 8.2-6.8 (m, 8 ar H), 5.64 (s, 2H, CH_2O), 3.90 (s, 3H, OCH_3).

Anal. Calcd. for $C_{15}H_{13}NO_5$: C, 62.71; H, 4.57; N, 4.88. Found: C, 62.32; H, 4.62; N, 4.77.

Ethyl α-(*o*-Nitrophenoxy)-*o*-toluate (**34**) and *o*-Nitrophenyl α-(*o*-Nitrophenoxy)-*o*-toluate (**35**).

By employing 360.0 g. (1.8 moles) of ethyl α-chloro-*o*-toluate, 291.0 g. (1.8 moles) of **5**, and 1500 ml. of DMF in the procedure for preparing **11**, there was obtained *via* ether extraction of the crude reaction product a 31% yield of the more soluble **34**, m.p. 96-98°, after recrystallization from cyclohexane; ν (mull) 1720 (s), 1610 (s), 1590 (s), 1515 (s), 1490 (s), 1430 (m) cm^{-1}; pmr (deuteriochloroform) δ 8.22-6.84 (m, 8 ar H), 5.62 (s, 2H, CH_2O), 4.35 (q, 2H, CH_2CH_3), 1.34 (t, 3H, CH_2CH_3).

Anal. Calcd. for $C_{16}H_{15}NO_5$: C, 63.77; H, 5.01; N, 4.64. Found: C, 63.80; H, 5.23; N, 4.78.

The ether-insoluble material was recrystallized from methanol to give **35** in 8% yield, m.p. 136-137°; ν (mull) 1725 (s) [Note: In phenyl acetate, carbonyl absorption is seen at 1765 cm^{-1}], 1620 (m), 1585 (m), 1525 (s), 1475 (m), 1455 (m), 1430 (m) cm^{-1}; pmr (deuteriochloroform) δ 8.56-6.80 (m, 12 ar H), 5.68 (s, 2H, CH_2O).

Anal. Calcd. for $C_{20}H_{14}N_2O_7$: C, 60.96; H, 3.58; N, 7.11; M.W. 394. Found: C, 61.23; H, 4.10; N, 6.83; M.W. (Rast) 391.

α-(*o*-Nitrophenoxy)-*o*-toluic Acid (**12**).

To a stirred suspension of 144.0 g. (0.5 mole) of **11** in 3600 ml. of 95% ethanol under reflux, was added, in 10 minutes, a solution of 31.0 g. (0.77 mole) of sodium hydroxide in 750 ml. of water. The heating under reflux was continued for 10 minutes and

the source of heat removed. To the mixture was added, rapidly, a solution of 920 ml. of concentrated hydrochloric acid in 750 ml. of water, followed by 2100 ml. of water, the whole cooled, and the solid filtered and dried to give 126.0 g. (92% yield) of **12**, m.p. 196-198°. An analytical sample was recrystallized from toluene and also melted at 196-198°; ν (mull) 2600-2325 (broad m), 1690 (s), 1610 (s), 1580 (s), 1520 (s), 1460 (s), 1400 (s), 1370 (s), 1340 (s) cm^{-1}; pmr (DMSO-d_6) δ 8.17-7.05 (m, 8 ar H, plus H of COO*H*), 5.7 (s, 2H of C*H*$_2$O).

Anal. Calcd. for $C_{14}H_{11}NO_5$: C, 61.53; H, 4.06; N, 5.12; N.E. 273. Found: C, 61.66; H, 4.02; N, 5.10; N.E. 271.

α-(*o*-Aminophenoxy)-*o*-toluic Acid (**13**).

A solution of 27.0 g. (0.1 mole) of **12** in 200 ml. of 0.5 *N* sodium hydroxide, 10 g. of Raney nickel (moist), and hydrogen (50 psi) were shaken for 3 hours, filtered, and the filtrate adjusted to *p*H 5.0. The solid that separated was filtered, washed, and dried to give 22.0 g. (90% yield) of **13**, m.p. 174-177°. An analytical sample, recrystallized from ethyl acetate, melted at 178-179°; ν (mull) 3360 (m), 3270 (m), 1680 (s), 1600 (s), 1565 (s), 1495 (s), 1480 (m), 1455 (m), 1430 (m) cm^{-1}; pmr (deuteriopyridine) δ 8.48 (s, H, COO*H*), 8.22 (s, 2H, NH_2), 8.12-6.53 (m, 8 ar H), 5.90 (s, 2H of C*H*$_2$O).

Anal. Calcd. for $C_{14}H_{13}NO_3$: N, 5.75; N.E. 243. Found: N, 6.08; N.E. (perchloric acid) 249; N.E. (potassium methoxide) 244.

Heating **13** with 98-100% formic acid gave the *N*-formyl derivative in 76% yield, m.p. 205-207° dec. after recrystallization from acetonitrile; ν (mull) 3330 (s), 2600 (s), 2470 (s), 1700 (s), 1640 (s), 1595 (s), 1540 (s), 1485 (m), 1445 (s) cm^{-1}; pmr (deuteriopyridine) δ 10.5 (s, H, COO*H*), 8.83 (t, H, C*H*O), 8.33 (t, H, N*H*), 7.38 (m, 8 ar H), 5.83 (s, 2H, C*H*$_2$O).

Anal. Calcd. for $C_{15}H_{13}NO_4$: N, 5.16; N.E., 271. Found: N, 5.43; N.E. (CH_3OK), 2.76.

Dibenz[*b,f*][1,4]oxazocin-11(12*H*)one (**14**).

To a solution of 16.0 g. (0.067 mole) of **13** in 1500 ml. of ethyl acetate, at 18°, was added, with stirring, 14.4 g. (0.075 mole) of DCC in 100 ml. of ethyl acetate. The mixture was stirred for 24 hours at 20°, filtered, and the filtrate was concentrated *in vacuo*. The residue was triturated with 120 ml. of absolute ethanol, the solid filtered and dried to give 5.8 g. (39% yield) of **14**, m.p. 210-211°. An analytical sample, recrystallized from 95% ethanol, melted unchanged at 210-211°; ν (chloroform) 3375 (s), 1675 (s), 1575 (m), 1325 cm^{-1}; pmr (deuteriochloroform) δ 7.92 (m, 1H of N*H*, exchanged by D_2O), 7.7-6.8 (m, 8 ar H), 5.51 (s, 2H, position-6).

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.62; H, 4.92; N, 6.21. Found: C, 74.93; H, 4.95; N, 6.41.

The absolute ethanol filtrate from the **14** obtained above, was concentrated *in vacuo*, the residue was stirred with 100 ml. of water, the solid filtered, and recrystallized first from absolute ethanol-ether and then from ligroin to give 2.6 g. (16% yield) of 1-[α-(*o*-aminophenoxy)-*o*-toluyl]-1,3-dicyclohexylurea, **15**, m.p. 113-114; ν (mull) 3470 (s), 3410 (s), 3365 (s), 1685 (s), 1650 (s), 1615 (s), 1515 (s), 1465 (s), 1450 (s), 1445 (s) cm^{-1}; pmr (deuteriochloroform) δ 7.33-6.76 (m, 8 ar H), 6.40 (m, NH of CN*H*C_6H_{11}), 5.21 (s, 2H of C*H*$_2$O), 5.83, 6.83 (m, each 1H, position-1 or 2 cyclohexyl groups), 2.0-1.0 (m, 20 H of C*H*$_2$ of 2 cyclohexyl groups), 3.88 (s, 2H of N*H*$_2$).

Anal. Calcd. for $C_{27}H_{35}N_3O_3$: C, 72.12; H, 7.84; N, 9.34; N.E., 450. Found: C, 72.33; H, 7.98; N, 9.47; N.E. (perchloric acid), 445.

12-[2-(Dimethylamino)ethyl]dibenz[*b,f*][1,4]oxazocin-11(12*H*)-one (**21**).

To a solution of 4.9 g. (0.02 mole) of **14** in 30 ml. of DMF at 20° was added 1.2 g. (0.025 mole) of 50% sodium hydride. The temperature rose spontaneously to 35°. Subsequently, the mixture was stirred for 0.5 hour, then heated for 10 minutes at 85°, cooled to 20°, and treated with 4.6 g. (0.03 mole) of 2-(dimethylamino)-ethyl bromide, in 5 minutes. The mixture was stirred and heated at 85° for 3 hours, cooled, filtered and the filtrate concentrated *in vacuo*. The residue was distributed between water and ether, the ether solution was extracted with 30 ml. of 0.5 *N* hydrochloric acid and the acid extracts worked up to give 4.0 g. of crude **21**, m.p. 102-104°. Recrystallization from ligroin gave 3.0 g. (50% yield) of **21**, m.p. 105-106°; ν (mull) 1650 (s), 1575 (m), 1490 (s), 1450 (s), 1395 (s) cm^{-1}; pmr (deuteriochloroform) δ 7.40-6.80 (m, 8 ar H), 5.83, 4.95 A_2B_{2q}, J=12, 2H, position-6), 4.55, 3.32 (2m, 2H of >NC*H*$_2$), 2.50 [m, 2H, C*H*$_2$N(CH_3)$_2$], 2.28 [s, 6H, N(C*H*$_3$)$_2$].

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.94; H, 6.80; N, 9.45. Found: C, 73.23; H, 6.72; N, 9.57.

6,11-Dihydro-12*H*-dibenz[*b,f*][1,4]oxazocine (**16**).

To a suspension of 4.8 g. (0.12 mole) of LAH in 1200 ml. of anhydrous ether at 20° was added, portionwise, during 1 hour, a total of 6.6 g. (0.0.03 mole) of **14**. The mixture was then stirred and heated under reflux for 1 hour, cooled, treated with 10 ml. of water and 20 ml. of 10% sodium hydroxide. The washed and dried ether solution was concentrated to give 6.0 g. of solid, m.p. 132-135°. Recrystallization from cyclohexane gave 5.0 g. (79% yield) of **16**, m.p. 133-135° ν (chloroform), 3400 (m), 1600 (m), 1500 (s), 1480 (s), 1450 (m) cm^{-1}; pmr (deuteriochloroform) δ 7.35-6.42 (m, 8 ar H), 5.33 (s, 2H, position-6), 4.58 (s, 2H, position-11), 3.90 (broad m, H of N*H*).

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.57; H, 6.19; N, 6.62; N.E., 211. Found: C, 79.89; H, 6.20; N, 6.73; N.E. (perchloric acid), 217.

6,11-Dihydro-12*H*-dibenz[*b,f*][1,4]oxazocine-12-carboxaldehyde (**17**).

A solution of 3.0 g. (0.014 mole) of **16** and 30 ml. of 97-100% formic acid was heated under reflux for 3 hours, cooled and poured into 500 ml. of ice water. The insoluble material was extracted into ether, the ether solution was washed, dried, concentrated and the residue recrystallized from diisopropyl ether to give 1.1 g. (33% yield) of **17**, m.p. 114-115°; ν (mull) 1670 (s), 1600 (m), 1580 (m), 1490 (s), 1460 (m), 1445 (s), 1425 (s), 1415 (m) cm^{-1}; pmr (deuteriochloroform) δ 8.45 (s, H, C*H*O), 7.4-6.84 (m, 8 ar H), 5.24 (s, 2H, position-11), 4.98 (s, 2H, position-6).

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.29; H, 5.48; N, 5.86. Found: C, 75.24; H, 5.53; N, 5.83.

12-[2-(Dimethylamino)ethyl]-6,11-dihydro-12*H*-dibenz[*b,f*][1,4], oxazocine (**22**).

To a slurry of 2.7 g. (0.072 mole) of LAH in 100 ml. of anhydrous ether was added a solution of 7.6 g. (0.024 mole) of **21** in 500 ml. of anhydrous ether. Subsequently, the course of the reaction was followed by decomposing an aliquot and examining the ether-soluble material for the presence of carbonyl absorption in the ir; reaction was complete after 12 hours of heating under reflux. Workup involved isolation *via* an acid-base transfer, and gave 3.7 g. of crude **22** as an oil; this, in 10 ml. of acetone, was treated with a solution of 2.4 g. (0.02 mole) of maleic acid in 12 ml. of acetone. The solid that separated was filtered and recrystallized from 2-propanol to give 1.1 g. (11% yield) of **22** · *maleate*,

m.p. 155-157°; ν (mull) 2840-2160 (broad, m), 1695 (m), 1615 (s), 1605 (s), 1580 (s), 1500 (s), 1455 (s), 1375 (s), 1360 (s) cm^{-1}; pmr (deuteriochloroform) δ 7.30-6.87 (m, 8 ar H), 6.26 (s, 2H of -CH:CH-), 5.22 (s, 2H, position-6), 4.48 (s, 2H, position-11), 3.74 (t, J = 7, 2H, >NCH_2) 3.17 (t, J = 7, 2H, CH_2N (CH_3)$_2$) 2.72 (s, 6H, -N(CH_3)$_2$).

Anal. Calcd. for $C_{18}H_{22}N_2O \cdot C_4H_4O_4$: C, 66.30; H, 6.57; N, 7.02; N.E., 199. Found: C, 66.31; H, 7.07; N, 6.84; N.E. (perchloric acid), 196; N.E. (potassium methoxide), 192.

12[2-(Diethylamino)ethyl]dibenz[*b,f*][1,4]oxazocin-11(12*H*)one (**36**).

The above alkylation procedure between 8.0 g. (0.35 mole) of **14**, 2.3 g. of 50% sodium hydride, 100 ml. of anhydrous toluene, 5 ml. of anhydrous DMF, and 7.0 g. (0.05 mole) of 2-(diethylamino)ethyl chloride in 50 ml. of anhydrous toluene gave 8.0 g. (69% yield) of **36**, m.p. 70-72° after recrystallization from petroleum ether; ν (mull) 1625 (s), 1595 (m), 1570 (m), 1490 (s), 1460 (m), 1450 (m), 1430 (m), 1390 (s), 1380 (s) cm^{-1}; pmr (deuteriochloroform) δ 7.53-6.80 (m, 8 ar H), 5.83, 5.00 (A_2B_{2q}, J = 12, 2H, position-6), 4.50, 3.40 (2m, 2H, >NCH_2), 2.84 [m, 2H, CH_2N(C_2H_5)$_2$], 2.60 [q, 4H, -N(CH_2CH_3)$_2$], 1.00 [t, 6H, -N(CH_2CH_3)$_2$].

Anal. Calcd. for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.46; N, 8.64; N.E., 324. Found: C, 73.85; H, 7.64; N, 8.51; N.E. (perchloric acid), 325.

12-[3-(Dimethylamino)propyl]dibenz[*b,f*][1,4]oxazocin-11(12*H*)-one (**37**).

To a suspension of 11.3 g. (0.05 mole) of **14** in 500 ml. of anhydrous toluene at 20° was added, in 5 minutes, 50 ml. of a 1.6 *N* solution of BuLi in hexane. The temperature rose spontaneously to 30°. The mixture was heated for 1 hour at 70°, the red-colored solution was cooled to 30°, and 10.0 g. (0.054 mole) of 3-(dimethylamino)propyl bromide in 100 ml. of anhydrous toluene was added. Finally, the mixture was heated for 6 hours at 85-90° and then worked up to give 4.9 g. (33% yield) of **37**, m.p. 98-99° after recrystallization from hexane; ν (mull) 1625 (s), 1600 (m), 1575 (m), 1495 (s), 1460 (s), 1450 (s), 1440 (s), 1430 (m), 1390 (s) cm^{-1}; pmr (deuteriochloroform) δ 7.46-6.83 (m, 8 ar H), 5.62, 5.00 (A_2B_{2q}, 2H, position-6), 4.40, 3.43 (m, 2H, >NCH_2), 2.35[t, 2H, CH_2N(CH_3)$_2$], 2.17 [s, 6H, N(CH_3)$_2$], 1.83 [m, 2H, CH_2CH_2N(CH_3)$_2$].

Anal. Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.51; H, 7.14; N, 9.03; N.E., 310. Found: C, 73.52; H, 7.35; N, 9.01; N.E. (perchloric acid), 318.

12-[3-(Diethylamino)propyl]dibenz[*b,f*][1,4]oxazocin-11(12*H*)-one (**38**).

The reaction of 4.0 g. (0.018 mole) of **14**, 1.2 g. (0.025 mole) of 50% sodium hydride (60 ml.) of anhydrous toluene, 4 ml. of anhydrous DMF, and 4.5 g. (0.03 mole) of 3-(diethylamino)propyl chloride, by the above procedure, gave 3.1 g. (50% yield) of **38**, m.p. 67-68°, after recrystallization from pentane; ν (mull) 1630 (s), 1590 (m), 1570 (m), 1490 (s), 1460 (m), 1435 (m), 1390 (s) cm^{-1}; pmr (deuteriochloroform) δ 7.58-6.80 (m, 8 ar H), 5.70, 5.06 (A_2B_{2q}, J = 15, 2H, position-6), 4.46, 3.45 (m, 3H, >NCH_2), 2.52 [m, 6H, 2H, CH_2N(CH_2CH_3)$_2$, 4H$_2$ (CH_2CH_3)], 1.80 [m, 2H, CH_2CH_2N(CH_2CH_3)$_2$], 1.00 [t, 6H, (CH_2CH_3)$_2$].

Anal. Calcd. for $C_{21}H_{26}N_2O_2$: C, 74.53; H, 7.74; N, 8.28; N.E., 338. Found: C, 74.82; H, 7.90; N, 8.54; N.E. (perchloric acid), 339.

12-Benzyl-6,12-dihydro-12*H*-dibenz[*b,f*][1,4]oxazocine (**19**).

To a solution of 0.90 g. (0.004 mole) of **16** in 40 ml. of anhydrous tetrahydrofuran at 20° was added, dropwise, 2.5 ml. of 1.6 *N* BuLi in hexane and the mixture stirred for 1 hour at 20°. Subsequently, 0.68 g. (0.004 mole) of benzyl bromide in 50 ml. of anhydrous tetrahydrofuran was added dropwise, and the whole stirred for 20 hours at 20°. The mixture was filtered, the filtrate was concentrated *in vacuo*, the residual oil was dissolved in ether, the ether solution was washed, dried and concentrated to give 0.70 g. of crude **19**; recrystallization from petroleum ether gave 0.40 g. (33% yield) of **19**, m.p. 70-72°; ν (mull), no NH, 1605 (s), 1500 (s), 1460 (s), 1450 (s), 1395 (m), 1370 (s), 1360 (s) cm^{-1}; pmr (deuteriochloroform) δ 7.45-6.65 (m, 13 ar H), 5.22 (s, 2H, position-6), 4.50, 4.43 (2s, 4H, position-11, 2H, $C_6H_5CH_2$).

Anal. Calcd. for $C_{21}H_{19}NO$: C, 83.64; H, 6.35; N, 4.64; N.E., 301. Found: C, 83.19; H, 6.81; N, 4.58; N.E. (perchloric acid), 298.

6,11-Dihydro-12*H*-dibenz[*b,f*][1,4]oxazocine-12-carboxamide (**26**).

A solution of 4.2 g. (0.02 mole) of **16** and 4.0 g. (0.04 mole) of triethylamine in 125 ml. of anhydrous toluene was treated with 4.0 g. (0.04 mole) of phosgene in 25 ml. of anhydrous toluene during 0.75 hour, maintaining the temperature at 5 to 10°. Afterwards, the mixture was stirred for 2 hours at 20°, filtered and the filtrate concentrated *in vacuo*. The residue, 5.4 g., was recrystallized from hexane to give 3.9 g. (70% yield) of the 12-carbonyl chloride (**24**), m.p. 113-114°; ν (mull) 1730 (s), 1600 (w), 1580 (w), 1495 (s), 1455 (m), 1380 (s) cm^{-1}; pmr (deuteriochloroform) δ 7.45-6.88 (m, 8 ar H), overlapping sextet, signals at 5.57, 5.33, 5.15, 4.94, 4.63, 5.62 (4H, 2 CH_2 groups, position-6 and -11).

Anal. Calcd. for $C_{15}H_{12}ClNO_2$: Cl, 12.95; N, 5.11. Found: Cl, 12.77; N, 5.14.

A mixture of 3.5 g. (0.012 mole) of **24** and 50 ml. of 3.2 *N* ethanolic ammonia, in a sealed tube, was heated for 18 hours at 95-100°. Workup gave 2.5 g. of solid, m.p. 145-152°. Recrystallization from toluene gave 1.2 g. (40% yield) of **26**, m.p. m.p. 151-153°; ν (mull) 3460 (s), 3315 (m), 3275 (m), 1665 (s), 1600 (s), 1590 (s), 1570 (s), 1490 (s), 1460 (s), 1435 (s), 1405 (s) cm^{-1}; pmr (deuteriochloroform) δ 7.37-6.77 (m, 8 ar H), 5.25 (s, 2H, position-11), 4.96, 4.86 (overlapping broad singlets, 4H, 2H, position-6, 2H, NH_2; equilibration with deuterium oxide eliminated signal at δ 4.86 and revealed the signal of the CH_2 at position-6 as a broad singlet at δ 4.94).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.84; H, 5.54; N, 11.01. Found: C, 70.80; H, 5.90; N, 10.94.

6,11-Dihydro-*N,N*-dimethyl-12*H*-dibenz[*b,f*][1,4]oxazocine-12-carboxamide (**27**).

To 3.0 g. (0.011 mole) of **24** in 100 ml. of benzene was added, at 20°, 1.8 g. (0.04 mole) of anhydrous dimethylamine in 10 ml. of benzene, dropwise. The reaction flask was subsequently stoppered, kept at 20° for 24 hours, the solid filtered, and the filtrate concentrated *in vacuo*. The residue, 3.1 g., m.p. 98-100°, was recrystallized from hexane to give 2.8 g. (80% yield) of **27**, m.p. 100-102°; ν (mull) 1645 (s), 1575 (m), 1485 (s), 1450 (s), 1380 (s), 1360 (s) cm^{-1}; pmr (deuteriochloroform) δ 7.33-6.84 (m, 8 ar H), 5.38 (s, 2H, position-11), 4.96 (s, 2H, position-6), 2.65 [s, 6H, N(CH_3)$_2$].

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.30; H, 6.42; N, 9.92. Found: C, 72.33; H, 6.35; N, 9.98.

N,N-Diethyl-6,11-dihydro-12*H*-dibenz[*b,f*][1,4]oxazocine-12-carboxamide (**28**).

The procedure for **27** was modified only in that 2.9 g. (0.04 mole) of diethylamine was used and this gave 2.5 g. (80% yield) of **28**, m.p. 138-140°, after recrystallization from hexane; ν (mull) 1640 (s), 1592 (m), 1575 (m), 1490 (s), 1470 (s), 1450 (s), 1410 (s), 1370 (s) cm^{-1}; pmr (deuteriochloroform) δ 7.30-6.80 (m, 8 ar H), 5.40 (s, 2H, position-11), 4.94 (s, 2H, position-6), 3.16 [q, 4H, $(CH_2CH_3)_2$], 0.8 [6H, $CH_2CH_3)_2$].

Anal. Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.60; H, 7.14; N, 9.03. Found: C, 73.85; H, 6.96; N, 9.08.

6,11-Dihydro-12*H*-dibenz[*b,f*][1,4]oxazocine-12-carboxylic Acid, Hydrazide (**29**).

To 10.0 ml. (0.2 mole) of 85% hydrazine hydrate in 10 ml. of methanol, at -5°, was added 5.0 g. (0.018 mole) of **22**, portionwise, during 1.5 hours. The temperature was maintained at 0° for 4.5 hours, and the mixture then poured into 150 ml. of cold water. The solid that separated was filtered and dried to give 3.7 g. of crude 29, m.p. 160-162°. Recrystallization from acetonitrile gave 3.1 g. (62% yield) of **29**, m.p. 160-162°; ν (mull) 3300 (s), 3270 (s), 3200 (s), 1655 (s), 1620 (s), 1575 (m), 1520 (s), 1510 (s), 1490 (s), 1470 (m), 1460 (s), 1445 (m), 1360 (s) cm^{-1}; pmr (deuteriochloroform) δ 7.40-6.87 (m, 8 ar H), 5.95 (broad s, H, N*H*), 5.19 (s, 2H, position-11), 5.00 (s, 2H, position-6), 3.56 (broad, s, 2H, NH_2).

Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.61. Found: C, 67.13; H, 5.88; N, 15.87.

12,12'-Carbonylbis[6,11-dihydro-12*H*-dibenz[*b,f*][1,4]oxazocine], (**25**).

To 2.1 g. (0.01 mole) of **16** in 100 ml. of anhydrous tetrahydrofuran was added a solution of 0.8 g. (0.013 mole) of *n*-BuLi in hexane (0.16*N*), in 5 minutes. A purple-red color developed as the temperature rose spontaneously to 40°. The mixture was stirred for 1 hour at room temperature, 1 hour at 50-55°, cooled to 30° and 2.7 g. (0.01 mole) of **24** in 40 ml. of tetrahydrofuran added in 3 minutes. Subsequently, the mixture was stirred for 16 hours at 20°, 4 hours at 45-50° and worked up to give 1.1 g. (24% yield) of **25**, m.p. 269-270° dec., after recrystallization from 1,2-dichloroethane; ν (mull) 1620 (s), 1595 (m), 1585 (m), 1570 (m), 1480 (s), 1440 (s), 1380 (s) cm^{-1}; pmr (trifluoroacetic acid) δ 7.43-6.57 (*m*, 16 ar H), 5.26 (d, J = 8, 4H, position-11), 4.94 (d, J = 12, 4H, position-6).

Anal. Calcd. for $C_{29}H_{24}N_2O_3$: C, 77.65; H, 5.39; N, 6.25. Found: C, 77.66; H, 5.49; N, 6.32.

6,11-Dihydro-12*H*-dibenz[*b,f*][1,4]oxazocine-12-carboxylic Acid, Methyl Ester (**23**).

The procedure was that for **25**, except that 30 g. (0.015 mole) of **16**, 1.5 g. (0.023 mole) of *n*-BuLi, and 2.8 g. (0.03 mole) of methyl chloroformate were used. The yield of **23**, m.p. 83-85°, after recrystallization from hexane, was 1.1 g. (27%); ν (mull) 1700 (s), 1600 (m), 1570 (m), 1490 (s), 1440 (s), 1420 (s) cm^{-1}; pmr (deuteriochloroform) δ 7.50-6.80 (m, 8 ar H), 5.18 (s, 2H, position-11), 4.84 (s, 2H, position-6), 3.65 (s, 3H, OCH_3).

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.35; H, 5.61; N, 5.20. Found: C, 71.26; H, 5.62; N, 5.11.

6,11-Dihydro-12*H*-dibenz[*b,f*][1,4]oxazocine-12-carboxylic Acid, Ester with Tropine (**30**).

A suspension of 1.0 g. (0.02 mole) of 50% sodium hydride in 50 ml. of benzene was treated dropwise with a solution of 2.7 g. (0.02 mole) of tropine in 100 ml. of benzene. The mixture was then stirred for 0.5 hour at 20°, 0.5 hour at 60°, cooled to 20°, and treated with 4.4 g. (0.016 mole) of **24**. The reaction mixture was heated under reflux for 24 hours, then cooled to 20°, washed free of Cl^-, dried and concentrated *in vacuo* to give 6.0 g. of residual oil. This, in ether, was extracted with 200 ml. of 0.5% hydrochloric acid, the acid extract was washed with ether, and the acid extract adjusted to *p*H 11 with powdered potassium carbonate. The crude *base*, isolated *via* ether extraction, weighed 4.0 g.; in solution, in 100 ml. of ether, this was treated with 2.3 g. (0.02 mole) of maleic acid in 400 ml. of ether. The crude *maleate*, 4.6 g. was recrystallized from 2-propanol to give 4.0 g. (76% yield) of **30** *maleate*, m.p. 152-154°; ν (mull) 2600-2200 (broad w), 1690 (s), 1630 (m), 1575 (m), 1490 (s), 1440 (s) cm^{-1}; pmr (deuterioacetonitrile) δ 7.57-6.50 (m, 8 ar H), 6.14 (s, 2H, -CH=CH-), 5.24 (s, 2H, position-6), 4.95 (broad s, 3H, one H, unassigned, 2H, position-11), 3.66, 2.33 (two broad s, each 2H, unassigned), 2.59 (s, 3H, NCH_3) 2.10-1.30 (m, 7H, unassigned).

Anal. Calcd. for $C_{23}H_{26}N_2O_3 \cdot C_4H_4O_4$: C, 65.88; H, 6.11; N, 5.67; N.E., 247. Found: C, 65.62; H, 6.21; N, 5.58; N.E. (perchloric acid), 251.

12-[(Dimethylamino)acetyl]-6,11-dihydro-12*H*-dibenz[*b,f*][1,4]-oxazocine (**32**).

To 9.0 g. (0.042 mole) of **16** and 9.0 g. (0.084 mole) of triethylamine in 400 ml. of anhydrous toluene, at 5°, was added 8.5 g. (0.084 mole) of chloracetyl chloride in 50 ml. of anhydrous toluene, dropwise, and with stirring. The stirring was then continued for 2 hours at 20°, the solid filtered, and the filtrate concentrated *in vacuo*. The residue was triturated with 50 ml. of petroleum ether and then recrystallized from ligroin to give 8.5 g. (70% yield) of **31**, m.p. 123-124°; ν (mull) 1675 (s), 1595 (m), 1575 (m), 1490 (s), 1455 (m), 1420 (m), 1400 (m), 1375 (s) cm^{-1}; pmr (deuteriochloroform) δ 7.40-6.80 (m, 8 ar H), 5.88, 4.32 (A_2B_{2q}, J = 15, 2H, position-11), 4.97, 4.50 (A_2B_{2q}, J = 11, 2H, position-6), 3.86 (s, 2H, CH_2Cl).

Anal. Calcd. for $C_{16}H_{14}ClNO_2$: Cl, 12.32; N, 4.86. Found: Cl, 12.58; N, 4.79.

A solution of 4.0 g. (0.014 mole) of **31** in 50 ml. of anhydrous benzene and 10.0 g. (0.22 mole) of anhydrous dimethylamine were kept in a stoppered flask for 48 hours at 20° and then heated under reflux for 2 hours. The cooled mixture was filtered, the filtrate was concentrated *in vacuo*, and the residue purified *via* an acid-base transfer. Recrystallization from hexane gave 2.8 g. (66% yield) of **32**, m.p. 95-96°; ν (mull) 1650 (s), 1595 (m), 1575 (m), 1490 (s), 1480 (m), 1450 (s), 1435 (s), 1400 (s), 1370 (s) cm^{-1}; pmr (deuteriochloroform) δ 7.36-6.74 (m, 8 ar H), 5.95, 4.26 (A_2B_{2q}, J = 15, 2H, position-11), 5.54, 4.96 (A_2B_{2q}, J = 12, 2H, position-6), 2.91 (s, 2H, CH_2), 2.2 [6H, $N(CH_3)_2$].

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.93; H, 6.80; N, 9.45; N.E., 296. Found: C, 72.99; H, 6.63; N, 9.74; N.E. (perchloric acid), 303.

12-(Dimethylcarbamoyl)dibenz[*b,f*][1,4]oxazocin-11(12*H*)one, (**33**).

To 0.56 g. (0.01 mole) of 50% sodium hydride in 100 ml. of anhydrous toluene at 25-30°, was added, portionwise, 2.5 g. (0.01 mole) of **14**. Following the addition, the mixture was stirred for 3 hours at 25°, and then 1.0 g. (0.01 mole) of dimethylcarbamoyl chloride in 10 ml. of anhydrous toluene was added, dropwise. A gelatinous mass separated initially, but this was soon replaced by a crystalline material. The mixture was kept 18 hours at 20°, the solid filtered, washed with water, and dried to give 2.5 g. of crude **33**, m.p. 223-225°. Recrystallization from absolute ethanol gave 2.1 g. (70% yield) of **33**, m.p. 224-226°; ν (mull) 1695 (s), 1670 (s), 1590 (s), 1460 (s), 1440 (m) cm^{-1}; pmr (deuteriochloroform) δ 7.50-6.90 (m, 8 ar H), 5.54, 5.26 (two broad multiplets, 2H,

position-6), 3.17 [s, 6H, -N(CH_3)$_2$].

Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.87; H, 5.78; N, 9.69..

Reaction of **1** with **5**; Isolation of α,α-Bis(*o*-nitrophenoxy)-*o*-xylene, (**6**).

A solution of 16.1 g. (0.1 mole) of **5** in 125 ml. of absolute ethanol and 150 ml. of DMF was added in **1** hour to a solution of 26.4 g. (0.1 mole) of **1** in 140 ml. of DMF, the mixture stirred for 24 hours at 20°, and concentrated *in vacuo*. The residue was triturated first with ether, then water, and the solid filtered and dried to give 9.0 g. of crude **6**, m.p. 125-132°. Recrystallization from acetonitrile gave 4.8 g. (25% yield) of **6**, m.p. 137-138°; ν (mull) no OH absorption, 1610 (s), 1580 (s), 1520 (s), 1485 (m), 1390 (m), 1345 (s) cm^{-1}; pmr (deuteriochloroform) δ 8.0-6.85 (m, 12 ar H), 5.52 (4H, two-*o*-CH_2O groups).

Anal. Calcd. for $C_{20}H_{16}N_2O_6$: C, 63.14; H, 4.29; N, 7.36. Found: C, 63.06; H, 4.46; N, 7.54.

Hydrogenation of Ethyl α-(*o*-Nitrophenoxy)-*o*-toluate (**34**).

A mixture of 6.0 g. (0.02 mole) of **34**, 200 ml. of methanol, and 1.0 g. of Raney nickel (moist) was shaken for 5 hours at 20° under 50 psi of hydrogen; only partial reduction occurred. At 40°, absorption of the theory of hydrogen required 4 additional hours. Workup of the filtered solution gave a tarry mass from which ethyl α-(*o*-aminophenoxy)-*o*-toluate (**37**) was isolated with difficulty as the *hydrochloride*, m.p. 178-180° dec. after recrystallization from acetonitrile; ν (mull) 1710 (s), 1625 (m), 1575 (m), 1500 (s), 1450 (s) cm^{-1}; pmr (deuteriochloroform), δ 10.33. 3H, NH_3^+, 8.40-6.80 (m, 8 ar H), 5.58 (s, 2H, CH_2O), 4.37 (q, 2H, CH_2CH_3), 1.39 (t, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{17}NO_3$·HCl: Cl, 11.51; N, 4.54; N.E., 308. Found: Cl, 11.22; N, 4.69; N.E. (perchloric acid) 307.

Saponification of the crude **37** gave crude **13**, and again this was purified with great difficulty to give, finally, **13**, with m.p. and mixture m.p. 178-179°.

Reaction of **1** with *o*-Hydroxyacetanilide. Isolation of 2′,2″-(*o*-Phenylenebismethoxy)bisacetanilide (**38**).

To 7.5 g. (0.05 mole) of *o*-hydroxyacetanilide and 13.2 g. (0.05 mole) of **1** in 200 ml. of absolute ethanol was added, in 0.25 hour, a solution of 2.7 g. (0.05 mole) of sodium methoxide in 25 ml. of absolute ethanol. The temperature rose spontaneously from 20 to 30° during the addition. The *p*H was then 10.0, and during 3 hours of stirring at room temperature, the *p*H decreased to 5.5 and a solid separated. This was filtered and dried to give 8.5 g. of solid, m.p. 161-163°. Recrystallization from ethyl acetate gave 5.0 g. (50% yield) of **38**, m.p. 165-167°; ν (mull) 3280 (s), 1660 (s), 1600 (s), 1545 (s), 1485 (s), 1420 (s), 1410 (s) cm^{-1}; pmr (deuteriochloroform) δ 8.20 (m, 2H, two N*H*), 7.90-6.84 (m, 12 ar H), 5.18 (s, 4H, two identical CH_2O), 1.92 (s, 6H, two identical CH_3CO).

Anal. Calcd. for $C_{24}H_{24}N_2O_4$: N, 6.59; Acetyl, 21.26. Found: N, 6.85; Acetyl, 21.01.

The recovery of unreacted **1** was 6.5 g. (49%).

o-Isoindolin-2-ylphenol (**4**) (a).

To 26.4 g. (0.1 mole) of **1** in 500 ml. of DMF at 90° was added, in 0.33 hour, 11.0 g. (0.10 mole) of **2** in 300 ml. of DMF. The mixture was stirred for 2 hours at 90°, concentrated *in vacuo*, and the residue triturated first with ether and then with acetonitrile to give 21.0 g. of crude **4**·HBr; an analytical sample recrystallized from acetonitrile metled at 233-240° gradual dec.; ν (mull) 3150 (m), 2650 (m), 2620 (m), 2600 (m), 1620 (m), 1590 (m), 1510 (m), 1475 (s), 1460 (s) cm^{-1}.

Anal. Calcd. for $C_{14}H_{13}NO$·HBr: Br, 27.35; N, 4.79; N.E., 211. Found: Br, 27.65; N, 4.88; N.E. (perchloric acid), 214.

To the *hydrobromide*, 19.0 g., 200 ml. of water, and 200 ml. of ether, under nitrogen, was added 100 ml. of 3% aqueous sodium hydroxide, dropwise. Subsequently, the ether layer was separated, washed, dried, and concentrated to give 12.0 g. of crude **4**, m.p. 118-120°. An analytical sample was recrystallized from cyclohexane and melted at 119-120°; a mixture m.p. with an authentic sample (4) was 119-120°; ν (mull) 3200 (m), 1600 (m), 1500 (s), 1450 (s) cm^{-1}; pmr (deuteriochloroform) δ 7.35-6.70 (m, 8 ar H), 6.52 (broad s, H, O*H*), 4.45 (s, 4H, two identical CH_2 groups).

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.57; H, 6.19; N, 6.62. Found: C, 79.67; H, 6.23; N, 6.82.

(b) When the same reaction conditions were employed with 13.2 g. (0.05 mole) of **1**, 6.9 g. (0.05 mole) of *o*-hydroxyformanilide, and 300 ml. of DMF, the crude reaction product was a tar from which 0.6 g. (6% yield) of **4** was isolated. The recovery of **1** was 10.0 g. (75%).

Reaction of α-Bromotoluic Acid (**7**) with Sodium o-Nitrophenoxide, (**5**); Isolation of Phthalide.

When a mixture of 4.3 g. (0.02 mole) of **7** and 3.2 g. (0.02 mole) of **5** in 160 ml. of acetonitrile was stirred at 20° for 3 hours and then concentrated, *o*-nitrophenol co-distilled with the acetonitrile. The residue was washed with water and dried *in vacuo;* during this procedure *o*-nitrophenol sublimed. The residue was recrystallized from diisopropyl ether to give 2.0 g. (74% yield) of phthalide, m.p. and mixture m.p. with an authentic sample, 72-74°; the respective ir spectra were superimposable. Phthalide was again the product, when the solvent was DMF instead of acetonitrile.

Methyl α-(*o*-Acetamidophenoxy)-*o*-toluate (**9**).

To 21.3 g. (0.113 mole) of **8** and 17.0 g. (0.113 mole) of *o*-hydroxyacetanilide in 300 ml. of absolute ethanol was added, at 20° in 0.25 hour, a solution of 6.1 g. (0.113 mole) of sodium methoxide in 65 ml. of absolute ethanol. The *p*H at this time was 9.8; 24 hours later, the *p*H was 8.2. Workup gave 22.0 g. (64% yield) of **9**, m.p. 114-115°, after recrystallization from cyclohexane; ν (mull) 3420 (s), 1715 (s), 1605 (m), 1595 (m), 1540 (s), 1495 (s), 1450 (s), 1435 (m); pmr (deuteriochloroform) δ 8.00 (m, H, N*H*), 7.70-6.80 (m, 8 ar H), 5.48 (s, 2H, CH_2O), 3.87 (s, 3H, OCH_3), 2.20 (s, 3H, $\overset{O}{\overset{\|}{C}}CH_3$).

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.58; H, 5.88; N, 4.69.

α-(*o*-Acetamidophenoxy)-*o*-toluic Acid (**10**).

A solution of 7.0 g. (0.02 mole) of **9** and 3.8 g. (0.07 mole) of 85% potassium hydroxide in 150 ml. of methanol, was heated under reflux for 3 hours and the reaction mixture worked up to give 4.7 g. (82% yield) of **10**, m.p. 181-182° after recrystallization from ethyl acetate; ν (mull) 3400 (s), 2670-2380 (broad s), 1660 (s), 1650 (m), 1580 (m), 1540 (s), 1490 (s), 1450 (m), 1410 (m) cm^{-1}; pmr (deuteriopyridine) 9.50 (broad s, H, CO_2H), 8.5 (s, H, N*H*), 7.83-6.80 (m, 8 ar H), 5.76 (s, 2H, CH_2O), 2.20 (s, 3H, $\overset{O}{\overset{\|}{C}}CH_3$).

When the reflux period in methanol was lengthened or when ethanol was used, at reflux, for 24 hours, degradation occurred, and the yield of **10** was decreased to 50%; only trace amounts of **13** were detected.

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(1) Presented in part at the Middle Atlantic Regional Meeting, A.C.S., Philadelphia, Pennsylvania, February 1-2, 1968.

(2) To whom correspondence should be addressed.

(3) H. L. Yale, F. A. Sowinski, and E. R. Spitzmiller, *J. Heterocyclic Chem.*, **9**, 899 (1972).

(4) A. H. Sommers, *J. Am. Chem. Soc.*, **78**, 2439 (1956) prepared this compound, m.p. 118-119°, by a totally different procedure. The authors are grateful to Dr. Sommers for a reference sample of his compound.

(5) H. L. Yale, B. Beer, Jelka Pluscec, and E. R. Spitzmiller, *J. Med. Chem.*, **13**, 713 (1970) have shown that the reaction of *o*-bromobenzyl bromide and *o*-aminophenol gave predominantly polymeric products along with small amounts of *N,N'-bis*(*o*-bromobenzyl)aminophenol; in contrast, *o*-hydroxyformanilide gave excellent yields of *o*-(*o*-bromobenzyloxy)formanilide.

(6) Cyclizations were attempted unsuccessfully (a) by heating **37** in boiling xylene, using calcium hydride to remove ethanol from the returning condensate [see H. L. Yale and M. Kalkstein, *J. Med. Chem.*, **10**, 334 (1967)]; (b) by heating **37** in cumene at 155°; (c) by heating **13** with thionyl chloride under reflux; (d) by heating **37**, neat, at 200-220°; and, (e) by sublimation of **13** at 0.05 mm and 80-180°.

(7) There are only two reports in the literature describing the use of DCC to effect intramolecular cyclizations that give an amide linkage; see M. Uskokovic and W. Wenner, Belg. Patent 645, 242, September 16, 1964 [*Chem. Abstr.*, **63**, 9972c (1965)] and, B. J. R. Nicolaus, E. Belasio, G. Pagoni, L. Mariani, and E. Testa, *Helv. Chim. Acta*, **48**, 1867 (1965).

(8) See Ref. 5.

(9) H. L. Yale and F. A. Sowinski, *J. Med. Chem.*, **10**, 1022 (1967).

(10) H. L. Yale *ibid.*, **11**, 396 (1968).

(11) The procedure employed to prepare this compound was modified from that reported by F. Gadient, F. Jucker, A. Lindemann, and M. Taeschler, [*Helv. Chim. Acta*, **14**, 1868 (1962)] who prepared the ethyl ester. The yield of crude product [n_D^{24} 1.5388, *Anal.* Calcd. Cl, 19.21. Found: Cl, 19.97] was quantitative and this material was used without further purification.