Benzoxocin and Benzoxonin Derivatives. Novel Groups of Terpenophenols with Central Nervous System Activity

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Condensation of carvone with olivetol gave a mixture of the two C-5 isomers of 5,6-dihydro-7-hydroxy-2-isopropyl-5-methyl-9-pentyl-2,6-methano-2*H*-1-benzoxocin-4(3*H*)-one (**2a** and **3a**) and their positional isomer **4**. These ketones were reduced to the respective alcohols, **5a**, **6a**, and **7a**, which were converted into the olefins **8a**, **9a**, **12**, and **13**. Compounds **2a** and **3a** were deoxygenated to **10** and **11a**. The benzoxonin **15a** was obtained from the condensation of olivetol with α-pinene. The 1,2-dimethylheptyl homologs (on C-9) of **2a**, **3a**, **5a**, **6a**, **8a**, **9a**, **11a**, and **15a** were also prepared. Several of these compounds produced CNS depression in rats at doses equal to or less than those required for the natural Δ^6- and Δ^1-tetrahydrocannabinols.

Very few central nervous system (CNS) agents are known which do not possess a nitrogen atom. The most conspicuous ones among them are the active cannabinoids,[1] both natural and synthetic. The structure–activity relationship in this series has been investigated in some detail[2,3] and it has been suggested[2] that a tricyclic ring system containing a benzopyran moiety is a requirement for CNS activity. It seemed of interest to construct novel related tricyclic terpenophenols (with or without a benzopyran moiety) and test them for CNS activity.

Condensation of carvone (**1**) with olivetol† in the presence of phosphorus oxychloride gave an oily mixture which was separated by chromatography into three new compounds: the two C-5 isomers of 5,6-dihydro-7-hydroxy-2-isopropyl-5-methyl-9-pentyl-2,6-methano-2*H*-1-benzoxocin-4(3*H*)-one (compounds **2a**, mp 161°, and **3a**, mp 181–182°) and a positional isomer, 5,6-dihydro-7-pentyl-2-isopropyl-5-methyl-9-hydroxy-2,6-methano-2*H*-1-benzoxocin-4(3*H*)-one (**4**, mp 108–109°). The structures of these compounds were deduced as follows. All three compounds, **2a**, **3a**, and **4**, have a molecular weight (as determined by mass spectrometry) of 330, indicating that they represent the products of 1:1 condensations of carvone (mol wt 150) with olivetol (mol wt 180). The unsaturated keto moiety in the starting material was transformed into a saturated keto grouping (ν_{max} 1720 cm^{-1}) indicating a possible Michael condensation (Scheme I).

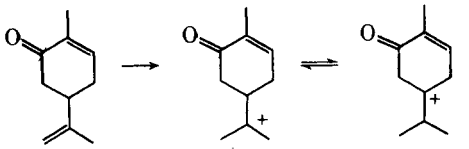
All three compounds give monoacetates, thus showing that one of the phenolic groups is not free and is presumably present as an ether. In the nmr spectrum there are no signals which can be interpreted as being due to protons α to oxygen atoms; hence, the ether linkage is at a tertiary position. In the nmr spectra only two aromatic protons are observed, indicating that one of the links between the terpenoid and the aromatic moieties is through one of the aromatic carbon atoms.

In all three compounds, a loss of an isopropyl group (*m/e* 287, 35% of M^+ in compound **2a**; 28% in **3a**; 71% in **4**) was observed in the mass spectra. We interpret this facile loss as an indication of the presence of a free isopropyl group. This assumption is supported by the nmr spectra: in all three compounds the peak assigned to the isopropyl methyls appears as a doublet.

The C-5 methyl group in all three compounds is a doublet. When the C-5 hydrogen in **2a** was replaced by a deuterium, this doublet collapsed to a singlet. The deuteration was performed by exchange with deuterium chloride in deuteriophosphoric acid. A collapse of the C-5 methyl group doublet to a singlet was also observed on irradiation of the C-5 proton at δ 2.85.

In all three compounds the benzylic C-6 proton is strongly deshielded (3.62 in **2a**, 3.40 in **3a**, 3.12 in **4**). Molecular models show that this proton is almost in the plane of the aromatic ring. In **4** the pentyl side chain apparently pushes the C-6 proton somewhat out of the plane, thus causing a dimunition of the deshielding effect. This placing of the pentyl side chain ortho to the terpene–olivetol link in **4** is supported by a comparison of the chemical shift of the C-6 proton in the free phenols **2a**, **3a**, and **4** and in their acetates. In **2a** and **3a** acetylation causes a marked upfield shift in the C-6 proton signal (to 3.20 in **2a** acetate; to 2.90 in **3a** acetate). In **4** no effect is observed. We interpret these findings as indicating that in **2a** and **3a** acetylation has a direct effect on the C-6 proton. In **4** the phenolic group is too distant to cause significant changes in the shifts of any terpenoid protons.

Compounds **2a**, **3a**, and **4** are racemates. When the reaction is undertaken with either (+)-carvone, $[\alpha]_D$ +58.5°, or (−)-carvone, $[\alpha]_D$ −54°, the same optically inactive products are obtained. Apparently the chirality of the molecule is destroyed through equilibration of the carbonium ion formed on the isopropyl side chain.



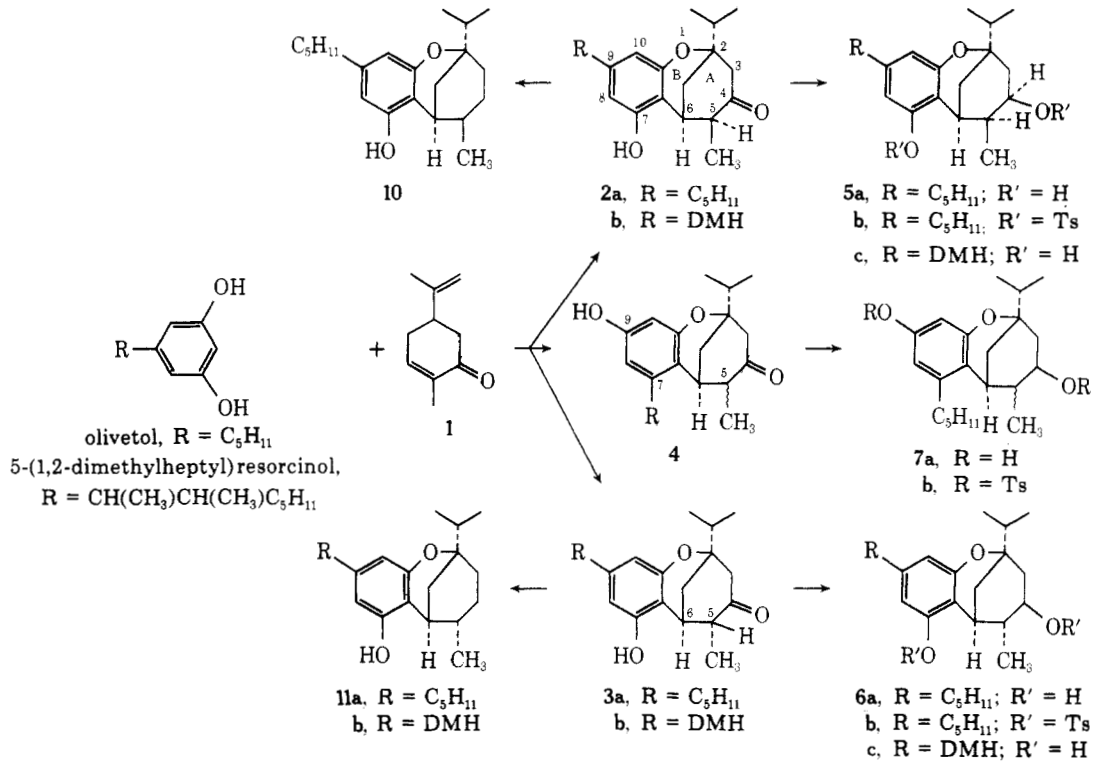
Compounds **2a** and **3a** differ in the stereochemistry of the C-5 chiral center only. The isopropyl group on C-2 and the hydrogen on C-6 have to be cis in **2a** and **3a** in order to allow the formation of both the keto-containing and the ether-containing rings (rings A and B, respectively) *via* the same bridgehead atoms C-2 and C-6. From molecular models it can be seen that the C-2 isopropyl group and the C-6 hydrogen have to be equatorial to both nonaromatic rings.

The C-5 hydrogen in **2a** is axial and cis to the C-6 hydrogen; in **3a** it is equatorial and trans. These configurations were deduced from the series of experiments described below.

Reduction of **2a** with lithium aluminum hydride gave a single product, the alcohol **5a**, mp 169–170°, in which the newly formed hydroxyl group is axial and syn to the pyran ring. The nucleophile (H^-) apparently attacks the carbonyl from the less hindered side (as seen from molecular models) leading to a hindered hydroxyl group as expected from Dauben's concept of "steric approach control."[4] The spectroscopic characteristics of **5a** are unexceptional. The

†A large number of compounds, mostly of the cannabinoid type, have been synthesized by condensation of terpenes with resorcinols. For a review see R. Mechoulam in ref 1, Chapter 1.

Scheme I



DMH indicates 1,2-dimethylheptyl

C-6 proton is shielded (as compared to the ketone **2a**) due to the elimination of the deshielding effect of the carbonyl group. Of some interest is the acetylation of **5a**. Under the standard acetylation conditions (acetic anhydride–pyridine, 24 hr at room temperature) only the phenolic hydroxyl underwent reaction giving a monoacetate (acetate methyl group at δ 2.25). The hindered hydroxyl group was acetylated on boiling with acetic anhydride–pyridine. The diacetate obtained showed a second, highly shielded acetate methyl group (δ 1.42). From molecular models it can be seen that the C-4 acetoxy group is indeed just above the phenolic ring. This observation gives additional support to the configurational assignment of the hydroxyl group. If the hydroxyl group was equatorial, the above described shielding effect would not have been observed.

Lithium aluminum hydride reduction of **3a** and **4** leads to the alcohols **6a**, mp 156–157°, and **7a**, mp 174–175°, respectively. The configuration of the hydroxyl group in both **6a** and **7a** is axial for the reasons presented for compound **5a**. The nmr spectra of the diacetates of both **6a** and **7a** show the presence of a highly shielded acetate methyl group (at δ 1.45).

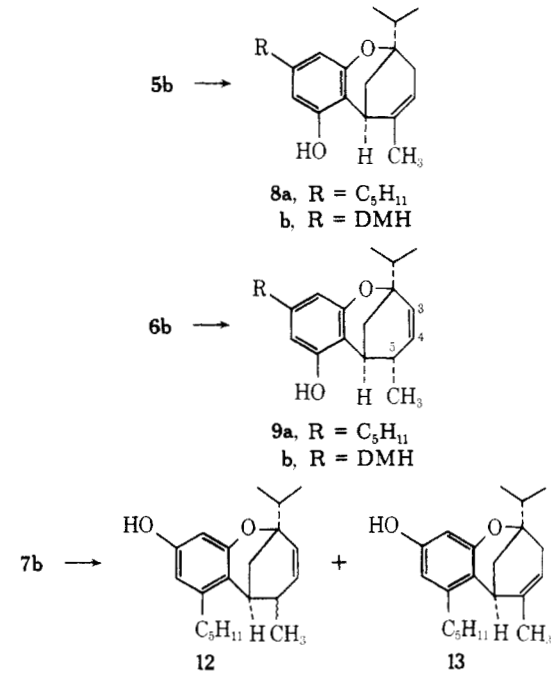
Tosylation of the alcohol **5a** (under standard conditions, for a period of 12 days) led to the ditosylate **5b**, mp 147°, which on treatment with potassium *tert*-amylate gave the olefin **8a**.

Tolsylation of the isomeric alcohol **6a** led to the ditosylate **6b**, mp 153°. The reaction was complete within 2 days (based on the disappearance of the starting material). Treatment with potassium *tert*-amylate gave the olefin **9a** (Scheme II).

In the reaction leading to **8a**, we were not able to detect the presence of **9a**. Likewise the formation of **9a** from **6b** did not produce isolable amounts of the isomer **8a**.

The above reactions indicate that the C-5 hydrogen in **5a** (and hence also in **2a**) is axial (*i.e.*, cis to the hydrogen on C-6) and that in **6a** it is equatorial. These conclusions are based on the well-established[5] tendency of elimination reactions to proceed in a trans-diaxial fashion with preference for the formation of more substituted double bonds. Thus in **5a** the elimination of the C-5 axial hydrogen is preferred to that of the C-3 hydrogens; however, in **6a** the C-5 hydrogen, apparently being equatorial, is sterically in an unfavorable conformation for such an elimination, which takes place now with the axial C-3 hydrogen.

Scheme II



The above conclusion is also supported by the considerably greater difficulty of the alcohol **5a** to undergo tosylation by comparison to **6a**. In **5a** the methyl group on C-5 is on the same side as the adjacent hydroxyl group and apparently contributes to the hindrance of its tosylation which is already high due to the aromatic moiety (as dis-

cussed above). In **6a** the methyl group at C-5 does not interfere with the reaction being trans to the hydroxyl group.

The configuration at C-5 in the compounds described above is consistent with the nmr data. In both **2a** and **5a** (in which the C-5 methyl group is equatorial) the equatorial C-6 proton is deshielded by *ca.* 0.2 ppm as compared to the same proton in **3a** and **6a** (in which the C-5 methyl group is axial). Such an effect by adjacent methyl groups is compatible with results reported by Booth.[6] In the set of compounds **10** and **11a** (see below) the same nmr relationship is retained.

The configuration of the C-5 hydrogen in **4** and **7a** was not determined. The ditosylate **7b** on treatment with potassium *tert*-amylate gave a mixture of the isomers **12** and **13.**

We tentatively suggest that **3a** is thermodynamically more stable than **2a.** This is indicated by the partial conversion of **2a** into **3a** by base. When **2a** was kept for 10 hr at room temperature in a solution containing 5% potassium hydroxide in aqueous methanol, 50% of **2a** was converted into **3a.** Under the same conditions only 5–6% of **3a** was converted into **2a.** It is difficult to reach equilibria conditions because of the formation of decomposition products. When the temperature was raised the situation became more complicated. Thus, boiling **2a** in 10% potassium hydroxide in aqueous methanol converts 60% of the material into carvacrol, olivetol, and polar materials; of the remaining material 64% is **3a** and 36% is **2a.** When **3a** is subjected to the same conditions, 75% is converted into other products; in the remaining material the ratio of **3a** to **2a** is essentially as above: 62% is **3a** and 38% is **2a.** A kinetic study of the various reactions taking place is needed in order to fully clarify the situation. Nevertheless, the above data tend to indicate that **3a** is the thermodynamically more stable isomer, although it contains an axial methyl group on C-5, while in **2a** the C-5 methyl group is equatorial. Examination of Dreiding models supports this conclusion; the C-5 methyl group in **3a** is less crowded than in **2a.**

Base treatment of **4** causes extensive decomposition. The only pure compound obtained was unchanged **4.** No epimerization was detected.

Ketones **2a** and **3a** led to the respective deoxy compounds **10** and **11a** by conversion into the thioketals, followed by dethioketalization with Raney nickel. Both **10** and **11a** exhibited the expected peaks in the spectral determinations (see Experimental Section). Of particular interest are (a) the disappearance of the carbonyl peak in the infrared; (b) the chemical shift of the C-6 proton, which is less deshielded than the corresponding proton in the ketones **2a** and **3a** [Apparently the C-6 proton in **2a** and **3a** is within the deshielding planes of both the aromatic ring and the carbonyl group. Removal of the latter causes an upfield shift (from 3.62 in **2a,** to 3.10 in **10;** from 3.40 in **3a** to 2.90 in **11a**). Molecular models indeed indicate that the C-6 proton falls almost in the plane of the carbonyl group]; (c) the facile loss of 43 mass units in the mass spectra indicating the cleavage of an isopropyl group.

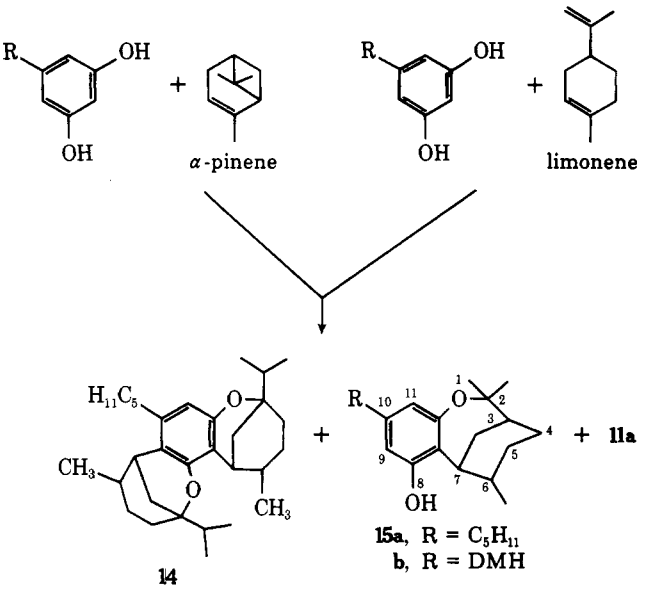
An entry into the same series of compounds can also be achieved from α-pinene. Reaction of this monoterpene with olivetol in the presence of phosphorus oxychloride produced a mixture which was separated into three components. The least polar component is the product of the condensation of two molecules of pinene with one of olivetol as shown by the molecular weight (452). The synthetic route and the spectral properties of this material suggest that it possesses structure **14** (Scheme III).

The next product (**15a**) eluted from the chromatography column was an optically inactive oil which had the same molecular weight as **10** and **11a** (*m/e* 316). The mass spectra of the three isomers are quite similar. The molecular peak and the one at *m/e* 231 are either base peaks or very strong ones. All three also have strong peaks at *m/e* 260 and 193. The major differences are (a) the appearance of a small peak (4.3%) in **15a** at $M^+ - 15$ which is absent in **10** and **11a.** This peak may indicate that while **15a** tends to lose a methyl group (at a tertiary position ?), in **10** and **11a** such a driving force is nonexistent; (b) the loss of 43 mass units (isopropyl group) is facile and predominates in **10** and **11a** (81 and 73%, respectively). In **15a** this loss is only 13%. We assume that the loss of an isopropyl group in **10** and **11a** is favored while in **15a** the relatively minor loss of 43 units may indicate a small amount of rearrangement to **10** or **11a** followed by cleavage. The nmr spectra of these three isomers are also closely related. Compound **15a** like **10** and **11a** has two aromatic protons, one hydroxyl group, one strongly deshielded benzylic proton (at δ 3.30, C-7 H), and two benzylic protons at δ 2.35 (side chain benzylic protons). The main difference is in the methyl group region. Compound **15a** has a large, sharp singlet at δ 1.30 (probably due to two methyl groups) which is absent in both **10** and **11a.** We suggest that this peak is due to the two methyl groups α to oxygen. By contrast, the δ 1.35 peak in both **10** and **11a** is short and very broad and probably represents a chance accumulation of protons. The methyl groups in **10** and **11a** (see Experimental Section) appear as sharp doublets upfield from δ 1.10. The most reasonable explanation for these differences is that the etheric oxygen in **15a** is attached to C-2 on the isopropyl side chain, forming a seven-membered ring: two methyl groups are then tertiary and α to the etheric oxygen. The tentative structure, 2,3,4,5,6,7-hexahydro-2,2-dimethyl-8-hydroxy-6-methyl-10-pentyl-3,7-methano-1-benzoxonin (**15a**), put forward is based on the assumption that no rearrangement of the carbon skeleton had taken place during the reaction.

A third product eluted in 19% yield was shown by direct comparison to be identical with **11a.**

Limonene can also serve as a starting material in the above reaction. Boiling limonene with olivetol in the presence of phosphorus oxychloride gives a mixture of compounds **14, 15a,** and **11a** but in a slightly different ratio

Scheme III



In **14** and **15** no stereochemical assignments
DMH indicates 1,2-dimethylheptyl

Table I. Dose Range of Activity in Rats

Compd	Relative act.[a]	Compd	Relative act.[a]
3a	+	**6a**	++
3b	+++	**6c**	++++
2a	+	**7a**	++
2b	+++	**15a**	+++
11a	++++	**15b**	+++
11b	++++	Δ^1-THC	++
5a	++++	Δ^6-THC	++
5c	+++		

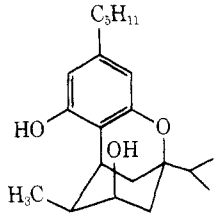
[a]Produced at least three of the following effects: moderate decrease in motor activity, low posture, ptosis, hypothermia, catalepsy, or vocalization to touch at oral doses of 1–10 mg/kg, ++++; 10–25 mg/kg, +++; 50 mg/kg, ++; 100–200 mg/kg, +.

than that obtained with pinene (with pinene, 35, 30, and 19%; with limonene, 35, 33, and 8%, respectively).

Using the above-described methods, the following 1,2-dimethylheptyl homologs (on C-9) were prepared: **2b, 3b, 5c, 6c, 8b, 9b, 15b.** The decision to synthesize these particular homologs was based on the known structure–activity relationships in the cannabinoid series.[2,3,7,8] Dimethylheptyl homologs of active tetrahydrocannabinols (THC's) are usually much more potent than the parent THC's or other homologs.

The results of examination of some of these compounds for their ability to produce overt effects in rats are presented in Table I. As can be seen, the presence of a dimethylheptyl side-chain group does not always give the more potent compound; thus the *n*-amyl-substituted compounds **11a, 5a,** and **15a** were equi- or more potent than the corresponding dimethylheptyl compounds. The most active of the benzoxocins and benzoxonins were equi- or more potent than the Δ^6- and Δ^1-THC's in our hands.

If the CNS activity of these benzoxocins and benzoxonins results from interaction with the same receptors as do the cannabinoids, then the presence of a benzopyran moiety is not necessary for activity. As mentioned heretofore, this has generally been considered to be a requirement for cannabinoid-type activity.[1] Also, while nearly all active cannabinoids are flat structures, molecular models indicate that the active benzoxocins and benzoxonins are not planar. (See stereochemical drawing of **5a** as an example.) Hence, flatness of the molecule is not a requirement for activity.



5a

Experimental Section

Pharmacology. Dose Range. Various dosages of the compound were administered orally to rats and overt effects were recorded over an extended period of time until the animals appeared normal. The drug was administered in solution in polyethylene glycol 400. The animals are observed for at least 6 hr on the day of treatment and at least once daily for 7–10 days after compound administration. In this test, a dose of 50 mg/kg po of Δ^6- or Δ^1-THC produces decreased motor activity, low body posture, vocalization when handled, and hypothermia. Some of the compounds in this study also produce catalepsy (*i.e.*, the animal remains in a set position when its feet are placed on four appropriately spaced No. 7 rubber stoppers for 30 sec).

Chemistry. The ir spectra were recorded on a Perkin-Elmer instrument, Model 137; the nmr spectra were measured on a Jeol-60H spectrometer and the uv spectra were measured on a Unicam S.P. 800 spectrophotometer. The mass spectra were measured on an Atlas CH4 instrument at 70 eV. Vapor-phase chromatography was conducted on a Packard Model 803 with a flame ionization detector on glass columns. Thin-layer chromatography was performed on silica gel chromatoplates. The microanalyses were done by the microanalytical department of the Hebrew University.

Reaction of Carvone with Olivetol. Carvone (1, 1.4 g, 9.3 mmol), $[\alpha]$D (EtOH) +58.5°, in 5 ml of benzene was mixed with olivetol (1.4 g, 7.8 mmol) and 0.5 g of phosphorus oxychloride. The solution was boiled for 2 hr. The reaction mixture was cooled and a saturated solution of sodium bicarbonate (50 ml) followed by ether (50 ml) was added. The organic layer was washed with a saturated solution of sodium chloride, dried over magnesium sulfate, and evaporated. The residue (2.8 g) was dissolved in petroleum ether–ether (10:1) (10 ml) and chromatographed over 125 g of silica gel. Fractions of 150 ml were collected. Each fraction was examined by tlc (elution with 10% ether in petroleum ether). Fractions with similar composition were combined. The following separation was achieved: (A) carvacrol (700 mg, 50% on the basis of carvone), elution with ether–petroleum ether (1:99); (B) a mixture of carbonyl-containing compounds (250 mg), which was not further investigated; (C) ketone **2a** (350 mg, 13.6% gross yield; 23.8% on the basis of reacted olivetol) eluted as a solid with 6% ether in petroleum ether; (D) a mixture of ketones **3a** and **4** (468 mg, 18.2% gross yield; 31.8% on the basis of reacted olivetol) eluted as a solid with 8% ether in petroleum ether; (E) unreacted olivetol (617 mg, 44%), eluted with 20% ether in petroleum ether.

Ketone 2a [5,6-dihydro-7-hydroxy-2-isopropyl-5-methyl-9-pentyl-2,6-methano-2*H*-1-benzoxocin-4(3*H*)-one (C-5 methyl equatorial)] was further purified by crystallization from ether–petroleum ether to yield pure **2a:** mp 161°; uv (EtOH) 275 nm (ϵ 1160), 282 (1125); ir ($CHCl_3$) 1720 cm^{-1}; nmr ($CDCl_3$) δ 0.90, 1.05 (d, J = 6 Hz, isopropyl methyls), 1.14 (d, J = 7.5 Hz, C-5 CH_3), 2.52 (br s, two C-3 H), 2.65–2.85 (C-5 H), 3.62 (m, C-6 H), 5.15 (OH, exchangeable with D_2O), 6.05, 6.20 (aromatic H), no olefinic protons or olefinic methyl groups; irradiation of C-5 H collapses the C-5 methyl doublet to a singlet; mass spectrum, 330 (M^+, molecular peak, 45), 287 (M^+ less C-2 isopropyl group, 35), 274 (12), 260 (100), 248 (60). *Anal.* ($C_{21}H_{30}O_3$) C, H. The acetate of **2a** is an oil: ir (CCl_4) 1720, 1780 cm^{-1}; nmr (CCl_4) δ 2.12 (acetate methyl), 3.20 (br m, C-6 H).

The mixture of ketones **3a** and **4** was separated by a further chromatography on 25 g of silica gel. Elution with 5% ether in petroleum ether gave first **5,6-dihydro-7-hydroxy-2-isopropyl-5-methyl-9-pentyl-2,6-methano-2*H*-1-benzoxocin-4-(3*H*)-one (C-5 methyl axial) (3a),** (380 mg, 14.8% gross yield; 25.4% on the basis of reacted olivetol): mp 181–182°; uv (EtOH) 280 nm (ϵ 1740); ir ($CHCl_3$) 1720 cm^{-1}; nmr ($CDCl_3$) δ 0.95, 1.05 (d, J = 6 Hz, isopropyl methyls), 1.12 (d, J = 8 Hz, C-5 CH_3), 3.40 (br, d, J = 18 Hz, C-6 H), 6.00, 6.10 (aromatic H), OH within aromatic proton region (evidenced by deuteration), no olefinic protons or olefinic methyl groups; mass spectrum, 330 (M^+, molecular peak, 35), 287 (M^+ less C-2 isopropyl group, 28), 274 (9), 260 (100), 248 (27). *Anal.* ($C_{21}H_{30}O_3$) C, H. The acetate of **3a** is an oil: ir (CCl_4) 1720, 1775 cm^{-1}; nmr (CCl_4) δ 2.20 (acetate methyl), 2.90 (br m, C-6 H). Further elution with the same solvent gave **5,6-dihydro-7-pentyl-2-isopropyl-5-methyl-9-hydroxy-2,6-methano-2*H*-1-benzoxocin-4-(3*H*)-one (4):** mp 108–109°; uv (EtOH) 282 nm (ϵ 2600); ir ($CHCl_3$) 1720 cm^{-1}; nmr ($CDCl_3$) δ 1.05 (d, J = 6 Hz, isopropyl methyls), 1.17 (d, J = 7.5 Hz, C-5 CH_3), 3.12 (br, $W_{1/2}$ = 7.5 Hz, C-6 H), 5.00 (OH, exchangeable with D_2O), 6.05, 6.10 (aromatic H), no olefinic protons or olefinic methyl groups; mass spectrum, 330 (M^+, molecular peak, 66), 287 (M^+ less C-2 isopropyl group, 71), 274 (7), 260 (100), 248 (64). *Anal.* ($C_{21}H_{30}O_3$) C, H. The acetate of **4** is an oil: ir (CCl_4) 1718, 1760 cm^{-1}; nmr (CCl_4) δ 2.15 (acetate methyl), 3.10 (br, $W_{1/2}$ = 7.5 Hz, C-6 H).

Base Treatment of 2a and 3a. Conditions A. Compound **2a** (52 mg, 0.158 mmol) was dissolved in methanol (3 ml). An aqueous solution (3 ml) of 10% potassium hydroxide was added and the reaction was left under nitrogen at room temperature (15°). After 2.5 hr an aliquot was analyzed. About 15% of **2a** had converted into **3a.** After 10 hr the ratio was 1:1, but some formation of decomposition products was observed. After 24 hr these products predominated.

Compound **3a** under the same conditions showed only *ca.* 2% conversion into **2a** after 2.5 hr and *ca.* 5–6% after 10 hr (however, decomposition products were formed). After 24 hr the decomposition products predominated.

Conditions B. Compound **2a** (110 mg, 0.334 mmol) was dis-

solved in methanol (3 ml). An aqueous solution (3 ml) of 20% potassium hydroxide was added and the reaction mixture was boiled for 3 hr. After the usual work-up the products of the reaction were chromatographed (tlc). Pure **2a** (16.8 mg, 15.2%) and **3a** (29.6 mg, 27%) were isolated. The remaining material consisted of unidentified decomposition products as well as carvarol and olivetol.

When compound **3a** (117 mg 0.355 mmol) was submitted to the same reaction conditions 11.9 mg (10.2%) of **2a** and 19.5 mg (16.6%) of **3a** were obtained.

Base Treatment of 4. When compound **4** was submitted to the same reaction conditions as those described above (conditions B) most of the material underwent decomposition. The only pure material obtained (15% of the starting material) was unchanged **4**. No isomerization products were detected.

Deuteration of 2a. A solution of DCl-D_3PO_4 was prepared as follows. Dry phosphorus trichloride (2 ml) was added to deuterated water (8 ml) over a period of 10 min. A 20% solution of DCl-D_3PO_4 was obtained, which was diluted to a 10% solution with deuterium oxide. Ketone **2a** (100 mg, 0.302 mmol) was suspended in 1 ml of the deuteration solution. Dry ether (1 ml) was added and the mixture was stirred at room temperature for 24 hr, extracted with ether, dried, and evaporated. The deuteration was then repeated. The compound isolated had a mp 164°, mmp (with authentic **2a**) 162–163°. On tlc deuterated **2a** was homogeneous. The mass spectrum showed the incorporation of 2, 3, 4, and 5 D atoms. The nmr spectrum differed from that of **2a** mainly in the collapse of the C-5 methyl doublet to a singlet.

Conversion of Ketone 2a into 3,4,5,6-Tetrahyro-7-hydroxy-2-isopropyl-5-methyl-9-pentyl-2,6-methano-2*H*-1-benzoxocin (C-5 Methyl Equatorial) (10). Ketone **2a** (1.4 g, 4.25 mmol) was dissolved in 5 ml of benzene. Ethanedithiol (0.3 ml) and 0.7 g of zinc chloride were added and the mixture was boiled 26 hr. Ice was added followed by a few drops of concentrated hydrochloric acid in acetone. The gelatinous mixture was extracted with ether (3 × 100 ml) and then with chloroform (3 × 100 ml). The organic solution was washed with a saturated sodium chloride solution, dried over magnesium sulfate, and evaporated to give 1.4 g of a mixture which showed no carbonyl peak in the infrared. Without further purification the crude thioketal was dissolved in 100 ml of methanol, 30 g of W-2 Raney nickel (in methanol) was added, and the mixture was boiled with stirring for 24 hr. The suspension was filtered through a filtered glass, which was then washed with methanol and ether. The combined filtrates were concentrated to give 700 mg (52.5%) of an oil which was purified by tlc. 3,4,5,6-Tetrahydro-7-hydroxy-2-isopropyl-5-methyl-9-pentyl-2,6-methano-2*H*-1-benzoxocin (C-5 methyl equatorial) (**10**) was obtained (310 mg, 23%) as an oil: uv (cyclohexane) 270 nm (ϵ 930), 280 (930); ir (CCl_4) no carbonyl peaks; nmr (CCl_4) δ 0.88, 1.00 (methyl groups), 1.35 (br), 1.70 (br, probably due to chance concentration of protons), 2.40 (br, m, benzylic), 3.10 (br, C-6 H), 4.40 (OH), 5.92, 6.10 (aromatic H); mass spectrum, 316 (M^+, 88), 273 (M^+ less 43 isopropyl group, 81), 260 (65), 231 (100), 193 (47), 120 (17).

The acetate of **5**, an oil, has nmr (CCl_4) δ 2.15 (3 H, acetate CH_3), 2.82 (br, C-6 H); ir (CCl_4) 1770 cm^{-1}.

Conversion of Ketone 3a into 3,4,5,6-Tetrahydro-7-hydroxy-2-isopropyl-5-methyl-9-pentyl-2,6-methano-2*H*-1-benzoxocin (C-5 Methyl Axial) (11a). The reaction was performed on **3a** (1.4 g, 4.25 mmol) exactly as described before for ketone **2a**. Compound **11a** (320 mg, 23.9%) was obtained as an oil: uv (cyclohexane) 270 nm (ϵ 660), 280 (660); ir (CCl_4) no carbonyl peaks; nmr (CCl_4) δ 0.98 (d, J = 7 Hz, isopropyl methyls), 1.09 (d, J = 7 Hz, C-5 CH_3), 1.35 (br), 1.65 (br, probably due to chance concentration of protons), 2.35 (br, m, benzylic), 2.90 (br, C-6 H), 4.50 (OH), 5.90, 6.10 (aromatic H); mass spectrum, 316 (M^+, 100), 314 (22), 271 (30), 273 (M^+ less 43 isopropyl group, 73), 260 (44), 231 (85), 220 (43), 193 (50).

The acetate of **6a**, an oil, has nmr (CCl_4) δ 2.17 (3 H, acetate CH_3), 2.68 (br, C-6 H); ir (CCl_4) 1780 cm^{-1}.

Reduction of Ketone 2a to 5,6-Dihydro-7-hydroxy-2-isopropyl-5-methyl-9-pentyl-2,6-methano-2*H*-1-benzoxocin-4(3*H*)-ol (C-5 Methyl Equatorial) (5a). Ketone **2a** (2.1 g, 6.35 mmol) dissolved in 20 ml of ether (dried on sodium metal) was dropped into a suspension of lithium aluminum hydride (3.0 g) in ether (100 ml) for 45 min and was boiled for another 24 hr; the reaction mixture was cooled with ice and a saturated solution of sodium sulfate was added slowly. The solution was acidified with hydrochloric acid (1:1) and extracted with ether (3 × 100 ml). The organic phase was washed with a saturated solution of sodium chloride, dried over magnesium sulfate, and evaporated to give 2.1 g of a solid which showed no carboxyl peak in the infrared. The residue was purified by column chromatography (silica gel, 82 g). Elution with ether–petroleum ether (15:85) gave **5,6-dihydro-7-hydroxy-2-isopropyl-5-methyl-9-pentyl-2,6-methano-2*H*-1-benzoxocin-4(3*H*)-ol (5a)** (2 g, 94%): mp 169–170° (ether–petroleum ether); uv (EtOH) 272 nm (ϵ 2170), 278 (2270); ir ($CHCl_3$) no carbonyl peaks; nmr ($CDCl_3$) δ 1.05 (d, J = 7 Hz, isopropyl methyls), 1.15 (d, J = 7 Hz, C-5 CH_3), 1.3, 1.4, 1.8 (br, probably due to chance concentration of protons), 2.45 (br, m, benzylic), 3.20 (br, C-6 H), 3.90 (C-4 H), 5.5 (br, OH), 6.12, 6.20 (aromatic H); mass spectrum, 332 (M^+, 100), 314 (M^+ less H_2O, 18), 299 (metastable peak), 272 (M^+ less 60, OH and isopropyl groups, 88), 232 (56), 194 (36). *Anal.* ($C_{21}H_{32}O_3$) C, H.

The monoacetate of **5a** was obtained by dissolving **5a** (100 mg, 0.305 mmol) in pyridine (10 ml) and acetic anhydride (0.4 ml) and keeping at room temperature for 12 hr. After the usual work-up the monoacetate of **5a** was obtained as an oil: nmr ($CDCl_3$) δ 1.25, 2.25 (3 H, acetate CH_3), 2.90 (br, C-6 H), 3.80 (br, C-4 H); ir ($CHCl_3$) 1770 cm^{-1}.

The diacetate of **5a** was obtained when the above described acetylation mixture was boiled for 4 hr. The oil obtained has ir ($CHCl_3$) 1770 and 1730 cm^{-1}; nmr (CCl_4) δ 1.42 (terpenoid acetate CH_3), 2.13 (aromatic acetate CH_3), 2.76 (C-6 H), 4.80 (H α to acetate).

Conversion of Ketone 3a into 5,6-Dihydro-7-hydroxy-2-isopropyl-5-methyl-9-pentyl-2,6-methano-2*H*-1-benzoxocin-4(3*H*)-ol (C-5 Methyl Axial) (6a). The reaction was performed on 2.4 g (0.725 mmol) of **3a** exactly as described before for ketone **2a**. Compound **6a** (2.3 g, 0.695 mmol, 96%) was obtained as a solid: mp 156–157° (ether–petroleum ether); uv (EtOH) 270 nm (ϵ 1560), 278 (1660); ir ($CHCl_3$) no carbonyl peak; nmr ($CDCl_3$) δ 0.85, 1.00 (d, J = 7 Hz, isopropyl methyls), 1.10 (d, J = 7.5 Hz, C-5 CH_3), 1.20, 1.25, 1.30 (probably due to chance concentration of protons), 2.30 (br, m, benzylic), 3.00 (br, C-6 H), 3.65 (C-4 H), 6.05, 6.15 (aromatic H); mass spectrum, 332 (M^+, 96), 314 (M^+ less H_2O, 37), 299 (metastable peak), 272 (M^+ less 60, OH and isopropyl, 100), 232 (45), 205 (25). *Anal.* ($C_{21}H_{32}O_3$) C, H.

The diacetate of **6a** is an oil: nmr (CCl_4) δ 1.45 and 2.20 (acetate methyls), 2.75 (br, C-6 H), 4.5 (br, C-4 H); ir ($CHCl_3$) 1730, 1760 cm^{-1}.

Conversion of Ketone 4 into 5,6-Dihydro-7-pentyl-2-isopropyl-5-methyl-9-hydroxy-2,6-methano-2*H*-1-benzoxocin-4(3*H*)-ol (7a). The reaction was performed on 200 mg (0.603 mmol) of **4** exactly as described for the two ketones **2a** and **3a**. Compound **7a** (190 mg, 95%) was obtained as a solid: mp 174–175° (ether–petroleum ether); uv (EtOH) 275 nm (ϵ 1550), 284 (1770); ir ($CHCl_3$) no carbonyl peak; nmr ($CDCl_3$) δ 1.05 (d, J = 7 Hz, isopropyl methyls), 1.15 (d, J = 7.5 Hz, C-5 CH_3), 1.45 (br, probably due to chance concentration of protons), 2.50 (br, m, benzylic), 2.90 (br, C-6 H), 3.75 (br, C-4 H), 3.85 (br, OH), 6.25, 6.30 (aromatic H); mass spectrum, 332 (M^+, 57), 314 (M^+ less H_2O), 299 (metastable peak), 272 (M^+ less 60, OH and isopropyl, 100), 232 (62). *Anal.* ($C_{21}H_{32}O_3$) C, H.

The diacetate of **7a** is an oil: nmr (CCl_4) δ 1.45, 2.15 (acetate CH_3 of the alcoholic and phenolic hydroxyls, respectively), 2.90 (br, C-6 H), 4.60 (br, C-4 H); ir ($CHCl_3$) 1740, 1780 cm^{-1}.

Comparison of Tlc and Glc Data of Compounds 2a–11a. Tlc (20% ether in petroleum ether): R_f of **2a**, 0.23; R_f of either **3a** and **4**, 0.15. Tlc (10% ether in petroleum ether): R_f of **10**, 0.32; R_f of **11a**, 0.27. Tlc (40% ether in petroleum ether): R_f of **5a**, 0.58; R_f of **6a**, 0.54; R_f of **7a**, 0.40. Glc (2% OV-17 on Chromosorb Q, N_2 flow 25 ml/min, column 8 ft 0.25 in., temperature 225°): retention time of **2a**, **3a**, and **4**, 5 min 36 sec; glc (as above except N_2 flow 40 ml/min; column 6 ft ⅛ in.; temperature 235°) retention time of compound **10** and **11a**, 3 min and 3 min 12 sec, respectively. Glc (conditions as previous) for compounds **5a**, **6a**, and **7a**: 10 min 24 sec, 10 min 48 sec, and 12 min 12 sec, respectively.

Conversion of 5a into 8a. To a solution of 1.5 g (4.5 mmol) of **5a** in 30 ml of pyridine, 10 g of *p*-toluenesulfonyl chloride (freshly crystallized from chloroform–petroleum ether) was added; the mixture was left at room temperature for 12 days, then poured into water (200 ml), and extracted three times with ether. The combined ether fractions were washed (3 × 100 ml) with 10% aqueous HCl and then with a saturated sodium chloride solution, dried over $MgSO_4$, and evaporated to give the ditosylate (2 g, 91.5%) **5b** as an oil, which was purified by chromatography on silica gel (60 g). Elution with ether–petroleum ether (2:8) gave 1.6 g (73.5%) of a solid: mp 147° (petroleum ether–ether); ir ($CHCl_3$) 1350, 1370 cm^{-1}; nmr (CCl_4) δ 2.37, 2.42 (s, two aromatic methyls), 4.75 (br, C-6 H), 7.1–7.8 (m, 8 aromatic protons). A portion of the ditosylate (1 g, 2.55 mmol) was added to a solution of 3.64 g

of potassium *tert*-amylate (freshly made by dissolving 1.5 g of potassium metal in 45 ml of *tert*-amyl alcohol near nitrogen, the excess of the alcohol evaporated under vacuum, and then 80 ml of dry toluene added and evaporated to dryness) in 80 ml of *tert*-amyl alcohol. The mixture was boiled under nitrogen for 6 hr and then poured into water (300 ml) and extracted three times with ether (200 ml); the combined extracts were washed with 10% aqueous HCl and then with a NaCl saturated solution and dried over $MgSO_4$. After evaporation, the obtained material (700 mg, 49.5%) was purified by plc (silica gel) eluted with (8:92) ether–petroleum ether to give pure **8a** as an oil: uv (EtOH) 275 (ϵ 1850), 281 (1860); ir (CCl_4) 1580, 1625 cm^{-1}; nmr (CCl_4) δ 0.87 (aliphatic CH_3), 0.98 (d, J = 7 Hz, isopropyl methyls), 1.76 (s, olefinic methyl), 2.23 (br, m, benzylic), 3.53 (t, J = 6 Hz, C-6 H), 4.83 (OH), 5.2 (br, C-4 H), 5.90, 6.20 (aromatic H); mass spectrum, 314 (M^+, 68), 271 (M^+ less 43 isopropyl group, 100), 258 (24), 218 (30), 193 (49).

The acetate of **8a**, an oil, has nmr (CCl_4) δ 2.25 (3 H, acetate CH_3), 3.20 (br, C-6 H), 5.30 (C-4 H); ir (CCl_4) 1770 cm^{-1}.

Conversion of 6a into 9a. To a solution of 580 mg (1.75 mmol) of **6a** in 10 ml of pyridine 3.0 g of *p*-toluenesulfonyl chloride was added; the mixture was left at room temperature for 48 hr and then poured into water and worked up as described above. Elution with ether–petroleum ether (1:9) from a silica gel column (20 g) gave (700 mg, 70%) pure ditosylate **6b**: mp 153° (petroleum ether–ether); ir ($CHCl_3$) 1350, 1370 cm^{-1}; nmr ($CDCl_3$) δ 2.42, 2.47 (s, two aromatic methyls), 4.60 (br, C-6 H), 7.2–7.9 (m, 8 aromatic protons). The ditosylate **6b** (700 mg, 1.45 mmol) reacted with a potassium *tert*-amylate solution as described above (using 2.5 g of potassium *tert*-amylate in 55 ml of *tert*-amyl alcohol). Purification of the obtained material on silica gel plc (elution with 8:92 ether–petroleum ether) gave **9a** (300 mg, 51.5%), an oil: uv (EtOH) 275 nm (ϵ 760), 281 (920); ir (CCl_4) 1580, 1625 cm^{-1}; nmr (CCl_4) δ 0.90 (aliphatic CH_3), 1.03 (d, J = 7 Hz, isopropyl methyls), 1.16 (d, J = 7.0 Hz, C-5 CH_3), 2.40 (br, m, benzylic), 3.07 (br C-6 H), 4.82 (OH), 5.5 (d, J = 11 Hz, C-3 H), 5.87 (dd, J = 11 Hz and J = 2.5 Hz, C-4 H), 6.05, 6.25 (aromatic H); mass spectrum, 314 (M^+, 47), 271 (M^+ less 43, 75), 220 (30), 205 (100), 201 (18), 193 (38). The acetate of **9a**, an oil, has nmr (CCl_4) δ 2.33 (3 H, acetate CH_3), 2.80 (br, C-6 H), 5.5 (d, J = 11 Hz, C-3 H), 5.87 (dd, J = 11 Hz and J = 2.5 Hz, C-4 H); ir (CCl_4) 1775 cm^{-1}.

Conversion of 7a to 12 and 13. To a solution of 750 mg (2.25 mmol) of **7a** in 15 ml of pyridine, *p*-toluenesulfonyl chloride (freshly crystallized from chloroform–petroleum ether) (5 g) was added; the mixture was left at room temperature for 14 days and then poured into water and worked up as described above. Elution with ether–petroleum ether (1:9) from a silica gel column (20 g) gave 500 mg (46%) of pure ditosylate **7b**: mp 142–143° (petroleum ether–ether); ir ($CHCl_3$) 1350, 1370 cm^{-1}; nmr ($CDCl_3$) δ 2.40 (s, two aromatic methyls), 4.70 (br, C-4), 7.2–7.9 (m, 8 aromatic protons). The ditosylate **7b** (500 mg, 1.05 mmol) was allowed to react with a potassium *tert*-amylate solution as described above (2.0 g of potassium *tert*-amylate in 45 ml of *tert*-amyl alcohol) to give a mixture of **12** and **13** (250 mg). The mixture (150 mg) was partly separated on a silica gel column (15 g) using ether–petroleum ether (1:99); 150 fractions of 25 ml were collected. Pure **12** was eluted first as an oil: uv (EtOH) 280 nm (ϵ 1170), 287 (1210); ir (CCl_4) 1580, 1620 cm^{-1}; nmr (CCl_4) δ 0.95 (d, J = 7 Hz, isopropyl methyls), 1.00 (d, J = 6 Hz, C-5 methyl), 2.25 (br, m benzylic), 2.75 (br, m, C-6 H), 5.3–5.7 (two vinylic protons), 6.00 (br, s, two aromatic H); mass spectrum, 314 (M^+, 94), 271 (M^+ less 43, 100), 201 (53), 193 (60), 149 (80), 137 (94). The next pure material eluted was **13**, an oil: uv (EtOH) 280 nm (ϵ 2070), 286 (2250); ir (CCl_4) 1580, 1620 cm^{-1}; nmr (CCl_4) δ 0.95 (d, J = 7 hz, isopropyl methyls), 1.65 (s, olefinic methyl), 2.20 (br, m, benzylic), 3.30 (br, C-6 H), 5.20 (br, vinylic proton), 6.00 (m, two aromatic H); mass spectrum, 314 (M^+, 97), 271 (M^+ less 43, 100), 201 (37), 193 (32), 137 (32).

Condensation of α-Pinene with Olivetol. α-Pinene (0.7 g, 5.15 mmol), $[\alpha]_D$ (EtOH) −41.6°, and olivetol (0.9 g, 5.0 mmol) were dissolved in 5 ml of benzene. Phosphorus oxychloride (0.3 g) was added and the solution was boiled for 2 hr. The cooled solution was neutralized with aqueous $NaHCO_3$ (50 ml) and extracted with ether. The etheric solution was chromatographed over silica gel (75 g). Elution with 2% ether in petroleum ether gave the double condensation product **14** (35%). Increase in the polarity of the elution solvent (5–10% ether in petroleum ether) yielded compound **15a** (30%); 12% ether in petroleum ether gave compound **11a** (19%). Further purification was made by preparative tlc. The pure compounds were characterized as follows.

1. **Double condensation product 14:** an oil; uv (cyclohexane) 276 nm (ϵ 2620), 284 (2720); nmr (CCl_4) δ 0.92, 1.02, 1.15, 1.27 (CH_3 groups), 2.30 (br, m, benzylic), 3.00 (br, C-6 H), 5.95 (aromatic H); mass spectrum, 452 (M^+, 71), 438 (9), 409 (M^+ less 43, isopropyl, 47.5), 396 (10), 367 (base peak).

2. **2,3,4,5,6,7-Hexahydro-2,2-dimethyl-8-hydroxy-6-methyl-10-pentyl-3,7-methano-1-benzoxonin (15a):** an oil; $[\alpha]_D$ (EtOH) 0°; uv (cyclohexane) 270 nm (ϵ 1120), 278 (1120); nmr (CCl_4) δ 0.95 (d, J = 7 Hz, C-6 CH_3), 1.30 (two C-2 methyl groups), 2.35 (br, m, benzylic), 3.30 (br, C-7 H), 4.60 (OH), 5.95, 6.12 (aromatic H); mass spectrum, 316 (M^+, 65), 301 (M^+ less 15, 4.3), 273 (13), 260 (31.4), 248 (15), 246 (28.5), 231 (100). The acetate of **15a** is an oil: nmr (CCl_4) δ 2.15 (3 H, acetate CH_3), 3.05 (br, C-7 H); ir 1780 cm^{-1}. The dinitrobenzoate of **15a** is a solid: mp 98–100°; nmr (CCl_4) δ 3.10 (C-7 H).

3. A further monocondensation product **11a** was found to be identical (ir, nmr, tlc, glc, and mass spectrum) with the compound obtained by deoxygenation of **3a** (*vide supra*).

Condensation of Limonene with Olivetol. The reaction was performed with limonene, $[\alpha]_D$ (EtOH) +113° as described for pinene using the same molar ratios of reagents. The reaction mixture was chromatographed to give the same compounds as in the previous experiment but in different yields (**14**, 35%; **15a**, 33%; **11a**, 8%).

Synthesis of 1,2-Dimethylheptyl Homologs. These homologs were prepared by the methods described for the pentyl derivatives, except that instead of olivetol (5-pentylresorcinol) the respective homolog was used, namely, 5-(1,2-dimethylheptyl)resorcinol. The same molar ratios of reagents and solvents were used as those described for the corresponding reactions with olivetol. The yields were comparable. Listed below are the compounds prepared and their physical constants.

5,6-Dihydro-7-hydroxy-2-isopropyl-5-methyl-9-(1,2-dimethylheptyl)-2,6-methano-2*H*-1-benzoxocin-4-(3*H*)-one (C-5 methyl axial) (3b): mp 134°; uv (EtOH) 272 nm (ϵ 1410), 281 (1360); ir (CCl_4) 1720 cm^{-1}; nmr (CCl_4) δ 1.00, 1.025, 1.10, 1.15, 1.27 (methyl groups), 1.90 (br), 2.15 (br), 2.45 (br), 3.175 (br C-6 H), 5.95, 6.05 (aromatic H); mass spectrum, 386 (M^+, molecular peak, 31), 315 (60), 287 (100).

5,6-Dihydro-7-hydroxy-2-isopropyl-5-methyl-9-(1,2-dimethylheptyl)-2,6-methano-2*H*-1-benzoxocin-4-(3*H*)-ol (5c): mp 95–96° (ether–petroleum ether); uv (EtOH) 270 nm (ϵ 1250), 280 (1340); ir ($CHCl_3$) no carbonyl peaks; nmr ($CDCl_3$) δ 0.75, 0.85, 0.95, 1.05, 1.20 (methyl groups) 1.75–2.00 (m), 2.40 (br), 3.15 (br, C-6 H), 3.85 (C-4 H), 5.5 (br, OH), 6.05, 6.15, (aromatic H); mol wt (mass spectrum) 388.

5,6-Dihydro-7-hydroxy-2-isopropyl-5-methyl-9-(1,2-dimethylheptyl)-2,6-methano-2*H*-1-benzoxocin-4(3*H*)-one (C-5 methyl equatorial) (2b): uv (EtOH) 272 nm (ϵ 1460), 281 (1460); ir (CCl_4) 1720 cm^{-1}; nmr (CCl_4) δ 0.70–1.30, 2.15 (br), 2.50 (br), 3.60 (br C-6 H), 6.00, 6.07 (aromatic H), no olefinic protons or olefinic methyl groups; mass spectrum, 386 (M^+, molecular peak, 34), 315 (68), 287 (100).

5,6-Dihydro-7-hydroxy-2-isopropyl-5-methyl-9-(1,2-dimethylheptyl)-2,6-methano-2*H*-1-benzoxocin-4-(3*H*)-ol (C-5 methyl axial) (6c): a solid; mp 134° (ether–petroleum ether); uv 270 nm (ϵ 1000), 278 (1040); ir ($CHCl_3$) no carbonyl peak; nmr ($CDCl_3$) δ 0.85, 0.90, 0.95, 1.10, 1.15, 1.20 (methyl groups), 1.65–2.00 (m), 3.00 (br, C-6 H), 3.60 (br, C-4 H), 6.05, 6.20 (aromatic H); mol wt (mass spectrum) 388.

Compound 8b: an oil; uv (EtOH) 275 nm (ϵ 1140), 281 (1180); nmr (CCl_4) δ 0.80, 0.90, 0.95, 1.05, 1.15 (methyl groups), 1.65–1.9 (m) 3.00 (br, C-6 H), 4.85 (OH), 5.37 (d, J = 9.5 Hz, C-3 H), 5.72 (d, d, J = 9.5 Hz, J = 4.5 Hz, C-4 H), 5.9, 6.10 (aromatic H); mol wt (mass spectrum) 370.

Compound 9b: an oil; uv (EtOH) 275 nm (ϵ 1720), 281 (1830); nmr (CCl_4) δ 0.80, 0.92, 1.0, 1.10 (aliphatic methyls), 1.80 (olefinic methyl methyl), 2.30 (br), 3.50 (t, J = 3.7 Hz, C-6 H), 4.67 (OH), 5.20 (br, C-4 H), 5.90, 6.12 (aromatic H); mol wt (mass spectrum) 370.

3,4,5,6-Tetrahydro-7-hydroxy-2-isopropyl-5-methyl-9-(1,2-dimethylheptyl)-2,6-methano-2*H*-1-benzoxocin (C-5 methyl axial) (11b): an oil; $[\alpha]_D$ (EtOH) 0°; uv (EtOH) 270 nm (ϵ 1130), 278 (1170); ir (CCl_4) no carbonyl peak; nmr (CCl_4) δ 0.75, 0.90, 1.00, 1.15, 1.45–1.75 (m), 2.90 (br, C-6 H), 4.75 (OH), 5.90, 6.10 (aromatic H); mol wt (mass spectrum) 372.

2,3,4,5,6,7-Hexahydro-2,2-dimethyl-8-hydroxy-6-methyl-10-(1,2-dimethylheptyl)-3,7-methano-1-benzoxonin (15b): an oil; $[\alpha]_D$ (EtOH) 0°; uv (EtOH) 270 nm (ϵ 1260), 278 (1280); nmr (CCl_4) δ 0.75, 0.90, 1.05, 1.15, 1.20, 1.30 (methyl groups), 1.40–1.80 (m), 2.25 (br), 3.30 (br, C-7 H), 4.55 (br, OH), 5.90, 6.10 (aromatic H); mol wt (mass spectrum) 372.

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Benzodiazepines. 4. 2-Oxyamino-5-phenyl-3*H*-1,4-benzodiazepines[1]

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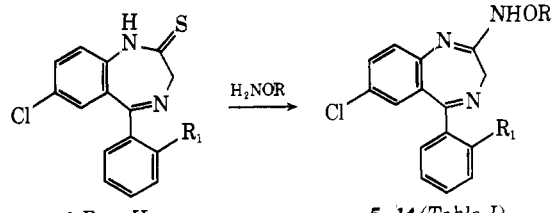
A series of 2-oxyamino-5-phenyl-3*H*-1,4-benzodiazepines has been prepared by the reaction of oxyamine derivatives with 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thiones. Pharmacologic testing in animals has shown that some of these compounds have interesting CNS depressant activity and suggests that they will have useful anxiolytic activity in man.

Because of our interest[1-3] in the potential antianxiety activity of new 1,4-benzodiazepine derivatives,[4-6] we have prepared a series of 5-phenyl-3*H*-1,4-benzodiazepines with oxyamino substituents at C-2.[7] Several of these compounds have excellent activity in our animal test systems which suggests that they will be useful anxiolytics in man.

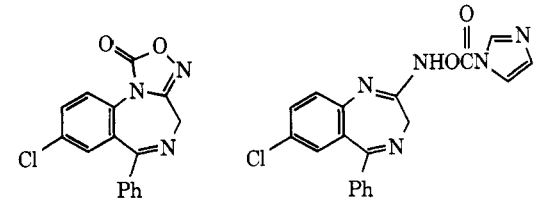
The preparation of 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thiones (*e.g.*, **1** and **2**) and the condensation of these compounds with amines to give 2-amino-5-phenyl-



1, R_1 = H
2, R_1 = Cl

5–14 (Table I)

3*H*-1,4-benzodiazepines have been described by Archer and Sternbach.[8] We have utilized this method for the preparation of the 2-oxyamino derivatives shown in Table I. When the oxygen was unsubstituted (*viz.* **5**, Table I) the derivative could be condensed with phosgene in the presence of triethylamine to give the 1*H*,4*H*-[1,2,4]oxadiazolo-[4,3-*a*][1,4]benzodiazepin-1-one (**3**).† It is interesting that the reaction of **5** with carbonyldiimidazole gave the imidazolide **4** rather than the expected cyclic product **3**. The reaction of **5** with acetic anhydride in pyridine gave the acetate ester **16**.



3 **4**

† A preliminary report of this reaction has been published; see ref 2.

Experimental Section

Chemistry. Melting points, taken in a capillary tube, are corrected. The structures of all compounds were supported by ir, uv, and nmr spectra. Ir spectra were determined in Nujol using a Perkin-Elmer Model 421 recording spectrophotometer. Uv spectra were determined in 95% EtOH using a Cary Model 14 spectrophotometer. Nmr spectra were recorded on a Varian Model A-60A; chemical shifts were recorded in parts per million downfield from Me_4Si. The silica gel used for chromatography was obtained from E. Merck A.G., Darmstadt, Germany. Skellysolve B (Sk B) is a commercial hexane, bp 60–70°, made by Skelly Oil Co., Kansas City, Mo.

7-Chloro-2-(hydroxyamino)-5-phenyl-3*H*-1,4-benzodiazepine (5). Procedure A. A mixture of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione (**1**, 14.4 g, 0.05 mol), hydroxylamine hydrochloride (4.55 g), $NaHCO_3$ (5.45 g), and MeOH (250 ml) was refluxed for 1.5 hr with a stream of N_2 bubbling through the mixture. The cooled mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (750 g) with Et_3N-MeOH-EtOAc (2:13:85) and the product was crystallized from EtOAc to give 4.92 g, mp 122.5–130°, and 3.38 g, mp 128–132°, of **5**.

***N*-(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)-*O*-(imidazol-1-ylcarbonyl)hydroxylamine (4).** A solution of carbonyldiimidazole (CDI, 2.62 g, 0.0162 mol) in dry THF (65 ml) was added to a stirred, ice-cold solution of **5** (2.32 g, 0.0081 mol) in THF (25 ml) and the resulting mixture was refluxed for 18 hr. Additional CDI (1.31 g, 0.0081 mol) was added and reflux was continued for 2 hr. The mixture was concentrated and the residue was suspended in H_2O. The solid was collected by filtration, washed with H_2O, dissolved in CH_2Cl_2, dried, concentrated, and crystallized from EtOAc–Skellysolve B to give 1.61 g (52.3%) of **4**, mp 105.5–106.5°. The analytical sample had mp 106.5°; uv end absorption, λ max 224.5 nm (ε 34,280), 250 (14,180), 300 (sh, 2350); ir 3140, 3120 (NH), sh 1795, 1770 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4.33, 5.03 (broad singlets, 2, C-3), 10.69 (s, 1, NH). *Anal.* ($C_{19}H_{14}ClN_5O_2$) C, H, Cl, N.

8-Chloro-6-phenyl-1*H*,4*H*-[1,2,4]oxadiazolo[4,3-*a*][1,4]benzodiazepin-1-one (3). A stirred solution of **5** (2.86 g, 0.0100 mol) and Et_3N (3.05 ml, 0.0220 mol) in dry toluene was cooled in an ice bath under N_2. Phosgene (0.795 ml, 0.011 mol) was evaporated into this mixture during 20 min. Excess phosgene was removed by bubbling a slow stream of N_2 through the mixture which was removed from the ice bath and allowed to stand at ambient temperature for 1 hr 15 min. The mixture was then poured into ice water and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was crystallized from EtOAc–Skellysolve B to give 1.56 g, mp 193–194°, and 0.80 g, mp 191–192° (75.6% yield), of **3**. The analytical sample