Benoxocin 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-2H-1-benzoxocin-4(3H)-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 benzoxin 15a was obtained from the condensation of olivetol with α-pinene. The 1,2-dimethylethyl 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 Δ9- and Δ1-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 detail2,3 and it has been suggested2 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 olivetol2 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-2H-1-benzoxocin-4(3H)-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-2H-1-benzoxocin-4(3H)-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 (νmax 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 deuteriodiphosphoric 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 benzyllic 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 diminution 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 in their acetates. In 2a and 3a acetylation has a direct effect on the C-6 proton; 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; [α]D +58.5°, or (-)-carvone; [α]D −54°, the same optically inactive products are obtained. Apparently the chirality of the molecule is destroyed through equilibration of the carboxonium ion formed on the isopropyl side chain.
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.

Tosylation 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 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.

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 hinderance 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 thiketals, followed by dethiolketolysis 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 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 monoterpen 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-6-methyl-10-pentyl-5,7-methano-1-benzoxoxin (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
were administered orally to rats and overt effects were recorded in this study also produce catalepsy. The animals are observed for at least 6 hr on the day of administration. In this test, a dose of 50 mg/kg PO of treatment and at least once daily for 7-10 days after compound over an extended period of time until the animals appeared normal. The drug was administered in solution in polyethylene glycol

Planar. (See stereochemical drawing of 5a that the active benzoxocins and benzoxonins are not cannabinoid-type activity.' This has generally been considered to be a requirement for activity. While nearly all active cannabinoids are flat structures, molecular models indicate that the active benzoxocins and benzoxinins are not planar. (See stereochemical drawing of 5a as an example.) Hence, flatness of the molecule is not a requirement for activity.

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 5a, or Δ4-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 CHF instrument at 70 eV. Gas-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.

Table I. Dose Range of Activity in Rats

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<th>Compound</th>
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<tr>
<td>3a</td>
<td>+</td>
<td>6a</td>
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<td>3b</td>
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<td>2a</td>
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<td>7a</td>
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<td>11a</td>
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<td>11b</td>
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<tr>
<td>5a</td>
<td>++++++</td>
<td>Δ4-THC</td>
<td>+</td>
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<td>5c</td>
<td>++++++</td>
<td>Δ9-THC</td>
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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, +.

Reaction of Carvone with Olivetol. Carvone (1, 1.4 g, 9.3 mmol, [α]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 distilled 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 (1:9); (B) a mixture of carbonyl-containing compounds (250 mg), which was not further investigated; (C) ketone 2a (350 mg, 13.6% gross yield; 25.8% on the basis of reacted olivetol) eluted as a solid with 6% ether in petroleum ether. (D) a mixture of ketones and the 15.2% 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-2H-1-benzoxocin-4(3H)-one (C-5 methyl compound)] was further purified by crystallization from petroleum ether to yield pure 2a: mp 161°; uv (EtOH) 276 nm (ε 1160), 282 (1125); ir (CHCl₃) 1720 cm⁻¹; nmr (CDCl₃) 6 0.90, 1.05 (d, J = 6 Hz, isopropyl methyl), 1.14, d, J = 7.5 Hz, C-5 CH₃), 2.52 (br s, two C-5 H), 2.65-2.85 (C-5 H), 3.62 (m, C-6 H, C-6 H), 5.15 (OH, exchangeable with D₂O), 6.05, 6.20 (aromatic H), 6.90, 7.05 (olefinic methyl or olefinic methyl groups; irradiation of C-5 H collapses the C-5 methyl doublet to a singlet; mass spectrum, 330 (M⁺, molecular peak), 287 (M⁺-C-2 isopropyl group, 35), 274 (126), 260 (100), 248 (60). Anal. (C₂₁H₃₀O₃) C, H. The acetate of 2a is an oil: ir (CCl₄) 1720, 1780 cm⁻¹; nmr (CDCl₃) 6 2.12 (acetate methyl), 3.20 (H, C-6 H). The mixture of ketones 3a and 4a was separated by a further chromatographic run 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-2H-1-benzoxocin-4(3H)-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) 281 (ε 1740); ir (CHCl₃) 1720 cm⁻¹; nmr (CDCl₃) 6 0.95, 1.05 (d, J = 6 Hz, isopropyl methyl), 1.12 (d, J = 8 Hz, C-5 CH₃), 3.40 (br, d, J = 18 Hz, C-6 H, 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⁺-C-2 isopropyl group, 28), 274 (9), 260 (100), 248 (27). Anal. (C₂₁H₂₉O₂) C, H. The acetate of 3a is an oil: ir (CCl₄) 1720, 1755 cm⁻¹; nmr (CDCl₃) 6 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-3-methyl-9-hydroxy-2,6-methano-2H-1-benzoxocin-4(3H)-one (3h): mp 188-189°; uv (EtOH) 282 (ε 2600); ir (CHCl₃) 1720 cm⁻¹; nmr (CDCl₃) 6 1.05 (d, J = 6 Hz, isopropyl methyl), 1.17 (d, J = 7.5 Hz, C-5 CH₃), 3.12 (br, W₁₂ = 7.5 Hz, C-6 H), 5.00 (OH, exchangeable with D₂O), 6.05, 6.10 (aromatic H), no olefinic protons or olefinic methyl groups; mass spectrum, 330 (M⁺, molecular peak, 56), 287 (M⁺-C-2 isopropyl group, 71), 274 (7), 260 (100), 248 (64). Anal. (C₂₁H₂₉O₂) C, H. The acetate of 3h is an oil: ir (CCl₄) 1718, 1760 cm⁻¹; nmr (CDCl₃) 6 2.15 (acetate methyl), 3.10 (br, W₁₂ = 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 carvalol 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 (18.1%) of 3a were chromatographed (tlc). Pure 3a (77.2 mg, 77%) was isolated. The remaining material consisted of unidentified decomposition products as well as carvalol and olivetol.

**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.** A solution of DCl-D3PO4 was prepared as follows. Dry phosphorus trichloride (2 ml) was added to deuterated water (8 ml) over a period of 10 min. The mass spectrum showed the incorporation of 2,3,4, and 5.

The acetate of 6a, an oil, has nmr (CHCl3) 6 2.15 (3 H, acetate CH3), 2.75 (br, C-6 H), 4.5 (br, C-4 H); ir (CHCl3) 1740, 1780 cm⁻¹. The acetate of 5, an oil, has nmr (CHCl3) 6 2.17 (3 H, acetate CH3), 2.13 (aromatic acetate CH3), 2.76 ((2-6 H), 4.80 (H); ir (CHCl3) 1770, 1730 cm⁻¹. The acetate of 8, an oil, has nmr (CDCl3) 6 2.17 (3 H, acetate CH3), 2.75 (br, C-6 H), 4.5 (br, C-4 H); ir (CHCl3) 1730, 1760 cm⁻¹.

Conversion of Ketone 2a into 3,4,5,6-Tetrahydro-7-hydroxy-2-isopropyl-5-methyl-9-pentyl-2,6-methano-2H-1-benzoxocin (C-5 Methyl Axial) (10). Ketone 2a (1.4 g, 4.25 mmol) was dissolved in 5 ml of benzene. Ethanethiol (0.3 ml) and 0.7 g of zinc chloride were added and the mixture was boiled 28 hr. Ice was added followed by a few drops of concentrated hydrochloric acid in acetone. The gelatinous mixture was extracted with ether-petroleum ether (15:85) and evaporated. The deuteration 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) 275 (3 1560), 278 (1560); ir (CHCl3) no carbonyl peak; nmr (CDCl3) 6 0.95, 1.00 (d, J = 7 Hz, isopropyl methyls), 1.20, 1.25, 1.3H (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 H₂O, 37), 299 (metastable peak), 272 (M⁻ less 60, OH and isopropyl), 100, 232 (45), 205 (25). Anal. (C₄₀H₆₀O₂) C, H.

The diacetate of 6a is an oil: nmr (CDCl3) 6 1.45, 2.15 (acetate methyls), 2.75 (br, C-6 H), 4.5 (br, C-4 H); ir (CHCl3) 1730, 1760 cm⁻¹.

Conversion of Ketone 4 into 5,6-Dihydro-7-pentyl-2-isopropyl-5-methyl-9-hydroxy-2,6-methano-2H-1-benzoxocin-4(3H)-ol (7a). The reaction was performed on 200 mg (0.685 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 (e 1550), 284 (1770); ir (CHCl3) no carbonyl peak; nmr (CDCl3) 6 0.95, 1.00 (d, J = 7 Hz, isopropyl methyls), 1.15 (d, J = 7.5 Hz, C-5 CH₃), 1.45 (br, probably due to chance concentration of protons), 2.30 (br, m, benzylic), 3.75 (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 H₂O, 37), 299 (metastable peak), 272 (M⁻ less 60, OH and isopropyl), 100, 232 (45), 205 (25). Anal. (C₂₀H₂₄O₂) C, H.

The diacetate of 7a is an oil: nmr (CDCl₃) 6 1.45, 2.15 (acetate methyls), 2.75 (br, C-6 H), 4.5 (br, C-4 H); ir (CHCl₃) 1730, 1760 cm⁻¹.

**Comparison of Tlc and Glc Data of Compounds 2a-11a.** Tlc (20% ether in petroleum ether): Rr of 2a, 0.23; Rr of either 3a and 4, 0.15. Tlc (10% ether in petroleum ether): Rr of 10, 0.32; Rr of 11a, 0.27. Tlc (40% ether in petroleum ether): Rr of 5a, 0.68; Rr of 6a, 0.54; Rr of 7a, 0.40. Glc (2% OV-17 on Chromosorb Q, N₂ flow 25 ml/min, column 8 °F 20.5 in., temperature 225°): retention time of 2a, 3a, and 4, 5 min 36 sec; glc (as above except N₂ flow 40 ml/min, column 6 ft 8 in.; temperature 235°) retention time of compound 10 and 11a, 3 min and 3 min 12 sec, respectively. Glc (preparation as previous) of 2a, 3a, 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 hr, 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 MgSO₄, and evaporated to give the diotosylate (2 g, 91%). 5b as a oil, which was purified by chromatography on silica gel (2.0 g), 0.7 x 10 cm) and eluted with ether-petroleum ether (4:3); yield 1.5 g (73.5%) of a solid: mp 147° (petroleum ether-ether); ir (CHCl₃) 1350, 1370 cm⁻¹; nmr (CDCl₃) 6 2.37, 2.42 (s, two aromatic methylyls), 4.75 (br, C-6 H), 7.1-7.8 (m, 8 aromatic protons). A portion of the diotosylate (1.5, 2.56 mmol) was added to a solution of 3.64 g
of potassium tert-amyate (freshly made by dissolving 1.5 g of potassium tert-amylate 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 MgSO4. After evaporation, the obtained material (700 mg, 49.5%) was purified by silica gel (silica gel) eluted with 8:92 ether-petroleum ether (1:9) to give pure 8a as an oil: uv (EtOH) 275 nm; ir (CCl4) 1580, 1625 cm-1; nmr (CDCl3) δ 0.87 (aliphatic CH3, 10); 3.07 (br, C-6 H), 5.5 (d, J = 6 Hz, isopropyl methyl), 2.25 (br, m, benzylic), 3.20 (C-6 H), 5.95, 6.00 (aromatic H); mass spectrum, 314 (M+, 32), 271 (M+ less 43, 100), 258 (24), 218 (32). The acetate of 8a, an oil, has nmr (CCl4) δ 2.33 (s, two aromatic methyls), 1.00 (d, J = 6 Hz, isopropyl methyl), 2.20 (br, m, benzylic), 3.50 (br, C-7 H), 4.55 (br, OH), 5.90, 6.10 (aromatic H); mol wt (mass spectrum) 388 (M+, molecular peak, 35). Synthesis of Limonene with Olivetol. The reaction was performed with limonene, [α]25D +113° as described for piniene 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%).

Condensation of Limonene with Olivetol. The reaction was performed with limonene, [α]25D +113° as described for piniene 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%).
Benzodiazepines. 4. 2-Oxyamino-5-phenyl-3H-1,4-benzodiazepines

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A series of 2-oxyamino-5-phenyl-3H-1,4-benzodiazepines has been prepared by the reaction of oxyamine derivatives with 1,3-dihydro-5-phenyl-2H-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 interest1-3 in the potential antianxiety activity of new 1,4-benzodiazepine derivatives,4-6 we have prepared a series of 5-phenyl-3H-1,4-benzodiazepines with oxyamino substituents at C-2. 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-2H-1,4-benzodiazepine-2-thiones (e.g., 1 and 2) and the condensation of these compounds with amines to give 2-amino-5-phenyl-3H-1,4-benzodiazepines has 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 1H,4H-[1,2,4]oxadiazolo[4,3-a][1,4]benzodiazepin-1-one (3) which is interesting that the reaction of 5 with carbonyldiimidazolide gave the imidazolide 4 rather than the expected cyclic product 3. The reaction of 5 with acetic anhydride in pyridine gave the acetate ester 6.

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 Cary Model 14 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&. 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-(hydroxamino)-5-phenyl-3H-1,4-benzodiazepine (5). Procedure A. A mixture of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-thione (1, 1.44 g, 0.05 mol), hydroxylamine hydrochloride (4.55 g, NaHCO3 (5.45 g), and MeOH (250 ml) was refluxed for 1.5 hr with a stream of N2 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 Et4N-MeOH-ETOAe (21:3:85) 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-3H-1,4-benzodiazepin-2-yl)-O-(imidazol-1-ylcarbonyl)hydroxylamine (4). A solution of carbonyldiimidazolide (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 H2O. The solid was collected by filtration, washed with H2O, dissolved in CH2Cl2, 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 294.5 nm (ε 34,280), 250 (14,180), 300 (sh, 2380); ir 3140, 3120 (NH), sh 1795, 1770 cm-1 (C=O); nmr (CDCl3) δ 4.33, 5.03 (broad singlets, 2, C-3, 10.69 (s, 1, NH). Anal. (C19H14ClN2O2) C, H, Cl, N.

8-Chloro-6-phenyl-1H-4H-[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 Et2N (3.05 ml, 0.0220 mol) in dry toluene was cooled 20° and the mixture was refluxed for 1 hr. The mixture was then poured into ice water and extracted with CHCl3. The extract was dried (Na2SO4) 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...