Substituted 5H-Dibenz[b,g]-1,4-oxazocines and Related Amino Acids with Antiinflammatory Activity

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During an investigation of the antiinflammatory properties of a number of tetracyclic derivatives of 6,8-dichlorodibenz[b,f]oxepin-10(11H)-one, the ring-expanded 1,3-dichloro-5H-dibenz[b,g]-1,4-oxazocine (9) was prepared and found to be of considerable pharmacological interest. It was subsequently found that the corresponding ring-opened amino acid 66, a close analogue of the antiinflammatory agent fenclofenac, also possessed significant antiinflammatory activity, superior both to the dibenzoxazocine and to fenclofenac. These findings prompted extensive synthetic programs in both areas, and a number of derivatives in the amino acid series showed potencies considerably in excess of the standard compound. These phenylacetic acids, however, were significantly more ulcerogenic than fenclofenac whereas the corresponding dibenzoxazocines showed few signs of ulcerogenicity at doses up to 1 g/kg.

In our continuing search for compounds of greater potency than fenclofenac,1 [2-(2,4-dichlorophenoxy)phenylacetic acid], derivatives of the ring-closed compound 6,8-dichlorodibenz[b,f]oxepin-10(11H)-one were prepared. One of these, 1,3-dichloro-6,7-dihydro-5H-dibenz[b,g]-1,4-oxazocine (9) was found not only to be twice as potent as fenclofenac in the adjuvant arthritis test but also to have no measurable ulcerogenic potential at doses up to 1 g/kg. This was considered to be a lead of considerable importance particularly as it was one of the few nonacidic compounds which showed activity in the adjuvant arthritis test. It was soon realized however that a metabolic breakdown to the corresponding 2-(6-amino-2,4-dichlorophenoxy)-phenylacetic acid (66) was possible and this was subsequently confirmed in metabolic studies in rats.2 The amino acid 66 showed enhanced potency over the corresponding oxazocine 9 in the adjuvant arthritis test, and extensive synthetic programs in both the amino acid and oxazocine series were initiated. This paper describes the synthesis and testing results for these compounds.

Chemistry. The route used to prepare all the NH-substituted oxazocines was that described in Scheme I. Cyclization of the readily available phenoxophenylacetic acids3 using polyphosphoric acid gave the corresponding oxepinones which were then treated with sodium azide in sulfuric acid to give the highly insoluble oxazocines. Without further purification these were reduced with lithium aluminum hydride to give the oxazocines, the majority of which were purified by crystallization of their hydrochloride salts. An alternative scheme involving the Beckman rearrangement of the oximes derived from the oxepinones failed to give satisfactory results. N-Methyl derivatives of the oxazocines were normally prepared by simple methylation as described in Scheme I, although in one case (compound 28), formylation and reduction was used. A potentially useful method involving the lithium aluminum hydride reduction of the corresponding N-methoxyoxazocine gave complex mixtures of products. Other N-alkyl, N-alkenyl, N-acyl, and N-benzyl derivatives of the oxazocines were prepared by standard procedures and representative examples are described in the Experimental Section.

Oxidation of the N-alkyl compounds 28, 31, and 33 with peracid gave the corresponding N-oxides 29, 32, and 34. After storage at room temperature for 1 month, compound 32 showed some signs of decomposition and further investigations revealed that heating the free base in ethyl acetate for 10 min resulted in complete decomposition to the styrene hydrate 1. The corresponding 1-chloro 29 and N-propyl 34 compounds appeared to be considerably more stable although even in these cases some degree of decomposition was noted after storage for several months.

2 Rance, M. J., unpublished results.

(2) Rance, M. J., unpublished results.
The synthesis of more conventional oxazocines via the re-oxidation of the corresponding allyl derivative

simple three-stage procedure described in Scheme I1

acid hydrolysis

in Scheme 11. Several attempts to adapt this method to

54.68. NT not tested.

(continued)

A dibenzoxazocine not listed in Table I, 1-chloro-6-methyl-6,7-dihydro-5H-dibenzo[b,g]-1,4-oxazocine (3) was prepared by the reductive cyclization of a nitro ketone derived from the osmium tetroxide/sodium periodate oxidation of the corresponding allyl derivative as described in Scheme II. Several attempts to adapt this method to the synthesis of more conventional oxazocines via the reductive cyclization of nitro aldehydes consistently afforded mixtures of products.

Two routes were used in the preparation of the primary amino acids. The first (method A, Scheme I) involved the acid hydrolysis of an oxazoline; the second involved the simple three-stage procedure described in Scheme II (method B). N-Methyl compounds were produced either by hydrolysis of the corresponding N-methyl oxazocinone or by the multistep route described in Scheme II. N,N-Dimethyl compounds were prepared by reductive methylation of the secondary amino acid.

Results and Discussion

The pharmacological results presented in Tables I–III are derived from the adjuvant arthritis test in rats and a measure of the minimum ulcerogenic dose (MUD) in the same species. Details of these tests are described in the Experimental Section.

The possibility that at least part of the activity of the dibenzoxazocines was the result of metabolic breakdown to the corresponding amino acid was recognized early in
Scheme I

\[
\begin{align*}
\text{R}^1 & \quad \text{O} \quad \text{R}^2 \\
& \quad \text{CH}_2\text{CO}_2\text{H} \\
& \quad \text{LiAIH}_4 \\
& \quad \text{KOH-Me} \\
& \quad \text{AcOH-HCl} \\
& \quad \text{METHOD A} \\
& \quad \text{NaH-Mel} \\
& \quad \text{or (i)HCOOH} \\
& \quad \text{Hg-ThF} \\
& \quad \text{LiAIH}_4 \\
& \quad \text{AcOH-HCl} \\
\end{align*}
\]

Scheme II

\[
\begin{align*}
\text{R}^1 & \quad \text{NO}_2 + \quad \text{R}^2 \quad \text{KO} \\
& \quad \text{CH}_2=\text{C}=\text{CH}_2 \\
& \quad \text{O}_2\text{O}_2=\text{HClO}_4 \\
& \quad \text{(R=CH}_2\text{)} \\
& \quad \text{Fe-AcOH} \\
& \quad \text{(R=H)} \\
& \quad \text{METHOD B} \\
& \quad \text{(i)KMnO}_4-\text{AcOH} \\
& \quad \text{(ii)H}_2\text{-Pd} \\
& \quad \text{(R=H)} \\
\end{align*}
\]

\[
\begin{align*}
& \quad \text{H}_2\text{-Pd} \\
& \quad \text{Ac}_2\text{O-CH}_3 \\
& \quad \text{KOH-CH}_3 \\
& \quad \text{KMnO}_4-\text{AcOH} \\
& \quad \text{AcOH-HCl} \\
& \quad \text{R}^1 & \quad \text{NH}_2 \quad \text{R}^2 \\
& \quad \text{CH}_2\text{CO}_2\text{H} \\
\end{align*}
\]
the program. Subsequent metabolic studies confirmed that the amino acid 66 was present in the plasma of rats dosed with the dibenzoxazines 9. As the obvious point of enzymic attack was the 6-position, compound 2 with a methyl group in that position was synthesized (Scheme II) and found to be totally inactive at 100 mg/kg, po, whereas the corresponding 6-H derivative 4 showed a 35% reduction in paw swelling at the same dose level. It seemed to us therefore that although it was possible that the dibenzoxazines themselves possessed some inherent antiinflammatory activity, two other factors might be important in defining the overall activity of these compounds. These were the predisposition of the dibenzoxazines for metabolism to an amino acid and the subsequent activity of that amino acid. It is reasonable to assume that the only compounds whose rate of metabolism to the amino acid might be reduced are those possessing an N-substituent which could provide some steric constraint to oxidation at C-6. However the necessary comparative data to assess the contribution of steric factors to overall activity is scarce. Only in the case of N-methyl compounds can valid comparisons be made and these derivatives (28 vs. 55 and 31 vs. 68) (Tables I and II) do show a good interseries correlation of activities. It is questionable however whether the relatively small size of the methyl group would have a significant effect on metabolism at C-6 and hence the
Table III. Substituted 2-(6-Nitrophenoxy)phenylacetic Acids and Derivatives

<table>
<thead>
<tr>
<th>no.</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>mp, °C</th>
<th>formula</th>
<th>anal.</th>
<th>rel to fenclofenac³</th>
<th>MUD, mg/kg,² po (24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>91</td>
<td>H</td>
<td>H</td>
<td>CO₂H</td>
<td>156-157</td>
<td>C₁₄H₁₂ClN₂O₅</td>
<td>C, H, N</td>
<td>1 (60)</td>
<td>2.0</td>
</tr>
<tr>
<td>92</td>
<td>2-Cl</td>
<td>H</td>
<td>CO₂H</td>
<td>153-154</td>
<td>C₁₄H₁₂ClN₂O₅</td>
<td>C, H, N</td>
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<td>1.1</td>
</tr>
<tr>
<td>93</td>
<td>2-Cl</td>
<td>H</td>
<td>CO₂Me</td>
<td>94-95</td>
<td>C₁₄H₁₃Cl₂N₂O₅</td>
<td>C, H, N</td>
<td>31 (25)</td>
<td>50-100</td>
</tr>
<tr>
<td>94</td>
<td>2-Cl</td>
<td>H</td>
<td>CO₂Bu¹</td>
<td>94-96</td>
<td>C₁₄H₁₃Cl₂N₂O₅</td>
<td>C, H, N</td>
<td>21 (50)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>95</td>
<td>2-Cl</td>
<td>H</td>
<td>CO₂Ph</td>
<td>138-139</td>
<td>C₁₄H₁₃Cl₂N₂O₅</td>
<td>C, H, N</td>
<td>30 (50)</td>
<td>1.0</td>
</tr>
<tr>
<td>96</td>
<td>2-Cl</td>
<td>H</td>
<td>CONH₂</td>
<td>163-165</td>
<td>C₁₄H₁₃Cl₂N₂O₅</td>
<td>C, H, N</td>
<td>36 (50)</td>
<td>1.1</td>
</tr>
<tr>
<td>97</td>
<td>2-Cl</td>
<td>H</td>
<td>CONH₂O</td>
<td>150-153</td>
<td>C₁₄H₁₃Cl₂N₂O₅</td>
<td>C, H, N</td>
<td>36 (50)</td>
<td>1.1</td>
</tr>
<tr>
<td>98</td>
<td>2-Cl</td>
<td>H</td>
<td>CH₂OH</td>
<td>71-72</td>
<td>C₁₄H₁₃Cl₂N₂O₅</td>
<td>C, H, N</td>
<td>37 (100)</td>
<td>50-100</td>
</tr>
<tr>
<td>99</td>
<td>2-Me</td>
<td>H</td>
<td>CO₂H</td>
<td>145-146</td>
<td>C₁₄H₁₁ClN₂O₅</td>
<td>C, H, N</td>
<td>28 (10)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>100</td>
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<td>H</td>
<td>CO₂H</td>
<td>104-105</td>
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<td>29 (100)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>101</td>
<td>2,3-Cl₂</td>
<td>H</td>
<td>CO₂H</td>
<td>162-163</td>
<td>C₁₄H₁₃Cl₂N₂O₅</td>
<td>C, H, N</td>
<td>25 (25)</td>
<td>1 (25)</td>
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<tr>
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<td>CO₂H</td>
<td>173</td>
<td>C₁₄H₁₃Cl₂N₂O₅</td>
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<td>1 (25)</td>
</tr>
<tr>
<td>103</td>
<td>3,5-Cl₂</td>
<td>H</td>
<td>CO₂H</td>
<td>156-157</td>
<td>C₁₄H₁₃Cl₂N₂O₅</td>
<td>C, H, N</td>
<td>34 (10)</td>
<td>2.9</td>
</tr>
<tr>
<td>104</td>
<td>2,5-Cl₂</td>
<td>H</td>
<td>CO₂H</td>
<td>198-199</td>
<td>C₁₄H₁₃Cl₂N₂O₅</td>
<td>C, H, N</td>
<td>34 (25)</td>
<td>3.3</td>
</tr>
<tr>
<td>105</td>
<td>2,3-Cl₂</td>
<td>H</td>
<td>CO₂H</td>
<td>186-187</td>
<td>C₁₄H₁₃Cl₂N₂O₅</td>
<td>C, H, N</td>
<td>17 (10)</td>
<td>0.8</td>
</tr>
<tr>
<td>106</td>
<td>2,4,5-Cl₃</td>
<td>H</td>
<td>CO₂H</td>
<td>164-165</td>
<td>C₁₄H₁₃Cl₂N₂O₅</td>
<td>C, H, N</td>
<td>30 (10)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>107</td>
<td>2-Cl</td>
<td>3-Cl</td>
<td>CO₂H</td>
<td>129-130</td>
<td>C₁₄H₁₃Cl₂N₂O₅</td>
<td>C, H, N</td>
<td>1 (25)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>108</td>
<td>2-Cl</td>
<td>3-Me</td>
<td>CO₂H</td>
<td>165-166</td>
<td>C₁₄H₁₃Cl₂N₂O₅</td>
<td>C, H, N</td>
<td>0 (25)</td>
<td>1 (25)</td>
</tr>
</tbody>
</table>

²See footnote a, Table I. ³See footnote b, Table I. ⁴See footnote c, Table I. ⁵See footnote d, Table II. ⁶See footnote e, Table II.

modest activities shown by the compounds 33, 35, 36, 41, and 42 (Table I) in which the N-substituent is considerably more bulky might reflect either the poor activity of their corresponding amino acids, for which data are not available, or steric constraint to metabolism. A further factor limiting the activity of the oxazocines is insolubility and this probably contributes significantly to the poor results obtained for compounds 35-40 and 43-46, all of which were highly insoluble. Furthermore, insolubility almost certainly plays a major role in the very low ulcerogenic potential of the oxazocines, none of which had a minimum ulcerogenic dose of less than 800 mg/kg.

It is clear from the pharmacological results of the amino acids presented in Table II that substitution in the amino-containing ring is essential for good activity. In the monosubstituted primary amino series (50-54, 56-59, and 62, 63), while not all substituents conferred significant activity, the 2-chloro 50, 2-methyl 59, and 4-trifluoromethyl 63 compounds were all substantially more potent than the unsubstituted compound 49, which was devoid of antiinflammatory activity. The importance of the 2- and 4-positions was highlighted in the disubstituted series where the introduction of a 4-chloro group in both the 2-chloro and 2-methyl series gave compounds with enhanced potencies over their monosubstituted analogues (66 vs. 50 and 80 vs. 59). Introduction of groups other than chloro in the 4-position of the 2-chloro compound appeared to cause a decrease in potency however (74 and 75). The 2,4-dichloro analogue 73 showed a surprising degree of activity and was relatively less ulcerogenic than its 2,4-dichloro counterpart.

Substituting the primary amino function with a methyl group in general gave compounds of increased potency (55 vs. 50, 60 vs. 59, and 68 vs. 66). In all cases where data are available, however, toxicity and/or ulcerogenicity was also considerably increased. Adding a further methyl group proved deleterious in the one case where valid comparisons are available (61 vs. 60).

Only three tri- and tetrasubstituted amino acids were synthesised (76-78), but of these, the two trichloro compounds 77 and 78 showed good potency and in the case of 78 a relatively low ulcerogenicity. This result is interesting as it reflects the apparently distinctive properties of tetrasubstitution in this ring system also shown by tetrachloro compounds described elsewhere.³

In the small series of compounds 83-88 with substituents in the phenylacetic ring, only two (compounds 85 and 89) showed significant activity.

The effects of esterification were variable; in some cases potency was retained (50 vs. 51, 66 vs. 67) and in others a sharp decrease occurred (68 vs. 69); as expected ulcerogenicity and/or toxicity was generally lower than for the corresponding acids.

A small number of 6-nitro compounds used as intermediates in the synthesis of the amino acids were also tested for antiinflammatory activity and several proved to be surprisingly potent (Table III). In particular the 2-methyl, 4-chloro compound 104 was found to be 3 times more potent than fenclofenac in a relative potency determination. However the small number of compounds synthesised precluded any meaningful structure-activity study, and further synthesis in this area was abandoned after the discouraging results from the oxazocine and amino acid series.

In conclusion, although the therapeutic ratios of a number of oxazocines are superior to that of the standard drug fenclofenac, the very poor solubility characteristics prevented further progression of these compounds. A number of N-oxides of the oxazocines were prepared as a means of enhancing solubility and hence absorption, but their inherent instability precluded further study. Sufficient evidence has been presented to suggest that antiinflammatory activity of the oxazocines in rats is due, at least in part, to their metabolic breakdown to the corresponding amino acids. Unfortunately, despite the high potencies associated with these compounds, their corre-

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spendingly high ulcerogenic potential gave therapeutic ratios which were inferior to fenclofenac, and consequently work was terminated in this area.

Experimental Section

Chemistry. Melting points were determined on a Buchi apparatus in glass capillary tubes and are uncorrected. IR and NMR spectra were recorded on Perkin-Elmer 283 and Varian Associates T60 instruments, respectively, and were consistent with the assigned structures. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values.

1-Dibenzoazocinones (Scheme 1). 1,3-Dichloro-6,7-dihydro-5H-dibenzo[b,g]-1,4-oxazocine Hydrochloride (9). 2-(2,4-Dichlorophenyl)phenyleacetic acid (40 g, 0.017 mol) was added to a stirred slurry of polyphosphoric acid (80 g) and the mixture was stirred at 80–90 °C for 0.5 h. The mixture was then cooled and poured into water, and the resulting precipitate was filtered off and dried to give 6,6-dichlorodibenzo[b,g][oxepin-10-(11H)-one: yield 5.5 g (74%); mp 91–92°C; IR(CBr3) ν max 1605, 1440 cm⁻¹.

Sodium azide (8.45 g, 0.13 mol) was added over 0.5 h to a stirred solution of the oxepinone (30 g, 0.11 mol) in concentrated H₂SO₄ (100 mL) and chloroform (500 mL) at 0 °C. After the addition, cooling of the mixture was continued for 3 h at room temperature. The chloroform layer was then discarded and the aqueous layer was poured onto ice, and the fine suspension which was produced was filtered off, washed with ethanol, and crystallized from dimethylformamide to give 1,3-dichloro-5H-dibenzo[b,g]-1,4-oxazocine-5-one: yield 19.9 g (62%); mp > 300°C. Satisfactory analyses could not be obtained for any of the dibenzoazocines due to their extreme insolubility and high melting points.

The oxazocine (5.7 g, 0.019 mol) was added portionwise over 0.5 h to a stirred suspension of lithium aluminum hydride (LiAlH₄, 1.7 g, 0.045 mol) in dry tetrahydrofuran (THF, 60 mL) at room temperature in an atmosphere of dry nitrogen. The stirred mixture was then heated under reflux for 4 h and cooled, and water was added dropwise with ice cooling. A saturated solution of sodium potassium tartrate was then added, and the resulting two layers were separated. The aqueous layer was extracted with ether, and the combined organic layers were washed with water, dried (MgSO₄), and evaporated to give a yellow solid, which was crystallized from dimethylformamide to give 1,3-dichloro-5H-dibenzo[b,g]-1,4-oxazocine-5-one: yield 3.1 g (58%); mp 159–160°C. The free base was crystallized from ethyl acetate/40–60°C petroleum to give 33: yield 12.5 g (59%). Anal. (C₁₇H₁₈Cl₂NO) C, H, N.

A solution of the N-formyl compound 30 (15.0 g, 0.058 mol) in dry THF (100 mL) was added dropwise to a stirred solution of borane/THF complex (1 M, 137 mL, 0.137 mol) at 0 °C under nitrogen. The mixture was stirred at this temperature for 0.5 h and then stirred for a further 6 h at room temperature. After which 6 N HCl (200 mL) was added. The resulting mixture was washed with ethyl acetate and the aqueous layer was then made basic with 880 aqueous ammonia solution followed by extraction with ether. The ether layer was washed with water, dried (MgSO₄), and evaporated to give a yellow solid, which was dissolved in the minimum quantity of dry ethanol. Addition of ethereal HCl precipitated the hydrochloride salt which was crystallized from ethanol/ether to give 28: yield 9.2 g (61%); mp 175–176°C. Anal. (C₁₇H₁₇ClNO·HCl) C, H, N.

1,3-Dichloro-6,7-dihydro-5-propyl-5H-dibenzo[b,g]-1,4-oxazocine (38). A mixture of the free base of the oxazocine hydrochloride 9 (15.0 g, 0.054 mol), propionaldehyde (52.5 mL, 0.73 mol), 10% palladium on charcoal (3.8 g), and ethanol (750 mL) was shaken vigorously under 3 atm of hydrogen at room temperature for 6 h. The catalyst was then filtered off and the ethanol was evaporated to give a brown oil. This was chromatographed on silica gel (70–230–mesh ASTM), eluting with 10% methanol in chloroform, and then with 10% methanol in ethyl acetate. The resulting fraction was washed with water, dried (MgSO₄), and evaporated to give a white solid, which was dissolved in the minimum quantity of dry ethanol. Addition of ethereal HCl precipitated the hydrochloride salt which was crystallized from ethanol/ether to give 34: yield 12.9 g (74%); mp 56–58°C. Anal. (C₁₇H₁₉ClNO·HCl) C, H, N.

1,3-Dichloro-6,7-dihydro-5-methyl-5H-dibenzo[b,g]-1,4-oxazocine (40). A mixture of the free base of the oxazocine hydrochloride 9 (5.0 g, 0.018 mol) in dry dioxane (75 mL) was cooled and stirred at 0 °C during the addition of a solution of methylthionium (1.9 M in ether, 11.5 mL, 0.022 mol). The solution was then stirred at 0°C for 0.5 h after which a solution of allyl bromide (2.6 g, 0.022 mol) in ether (25 mL) was added dropwise at 0°C. After a further 0.5 h at this temperature the mixture was allowed to warm to room temperature and stirred for 48 h. The mixture was then evaporated and the residue partitioned between ether and water. The organic layer was dried (MgSO₄), and evaporated to give a solid which was chromatographed on silica gel (70–230–mesh ASTM), eluting with 40–60°C petroleum. The white solid which was eluted was crystallized from 40–60°C petroleum to give 35: yield 3.8 g (66%); mp 74°C. Anal. (C₁₇H₁₇ClNO) C, H, N.

1,3-Dichloro-6,7-dihydro-5-fluorotolueno[b,g]-1,4-oxazocine (45). A solution of the free base of the oxazocine hydrochloride 9 (5.0 g, 0.010 mol) in dry dioxane (75 mL) was cooled and stirred at 0 °C during the dropwise addition of a solution of methyllithium (1.9 M in ether, 11.5 mL, 0.022 mol). The solution was then stirred at 0°C for 0.5 h after which a solution of allyl bromide (2.6 g, 0.022 mol) in ether (25 mL) was added dropwise at 0°C. After a further 0.5 h at this temperature the mixture was allowed to warm to room temperature and stirred for 48 h. The mixture was then evaporated and the residue partitioned between ether and water. The organic layer was dried (MgSO₄), and evaporated to give a solid which was chromatographed on silica gel (70–230–mesh ASTM), eluting with 40–60°C petroleum. The white solid which was eluted was crystallized from 40–60°C petroleum to give 35: yield 3.8 g (66%); mp 74°C. Anal. (C₁₇H₁₇ClNO) C, H, N.

1,3-Dichloro-6,7-dihydro-5-ethyl-5H-dibenzo[b,g]-1,4-oxazocine-5-carboxylate (43). Sodium ethoxide (2.07 g, 0.03 mol) was added to dry methanol (100 mL), and the mixture was heated under reflux for 10 min in an atmosphere of dry nitrogen. The mixture was then poured into ice/water and extracted with ethyl acetate. The organic phase was washed with water, dried (MgSO₄), and evaporated to give a yellow solid which was crystallized from ethanol/ether to give 32: yield 0.7 g (44%); mp 147–149°C. Anal. (C₁₇H₁₇Cl₂NO₂·HCl) C, H, N.

2-(2,4-Dichlorophenyl)methanone (37). A solution of phenone (12.5% w/w in toluene, 46 mL, 0.068 mol) in dry ether (126 mL) was stirred and cooled at 5–7°C during the dropwise addition of a solution of the free base of the oxazocine hydrochloride 9 (7.0 g, 0.025 mol) in ether (130 mL) and triethylamine (2.5 g, 0.025 mol). The mixture was stirred at this temperature for 0.5 h and then at room temperature for 2 h at room temperature. The precipitated solid was filtered off and washed with ether, and the combined organic layers were evaporated. The resulting yellow solid was crystallized from 40–60°C petroleum to give 37: yield 5.0 g (59%); mp 98–100°C. Anal. (C₁₇H₁₃ClNO) C, H, N.
and evaporated to give gel (70-230-mesh ASTM), eluting with chloroform, to give a white solid which was triturated with 40-60 °C petroleum giving 1-acetate, and the organic layers were combined, dried (MgSO₄), osmium tetroxide (catalytic quantity) and aqueous dioxane (3:1, g (100%); IR (thin film) then dried, and evaporated to give crude 3-[2-(2-chloro-6-nitrophenoxy)phenyl]-2-methylprop-1-ene

The ether layer was washed with 2 N NaOH solution and water, cooling, the mixture was partitioned between ether and water. The resulting precipitate was filtered off and the organic layer was stirred and heated at 115 °C under nitrogen for 4.5 h. After the mixture was stirred for 3 h at 0 °C, further quantities of triethylamine (3.5 g, 0.035 mol) and HCl to give 81: yield 2.4 g (14%); mp 174-175 °C. Anal. (C₁₅H₁₄ClNO) C, H, N.

2,4-Chloro-2-methyl-1-(methylamino)phenyloxenacetic Acid (81). A suspension of 3-chloro-1-methyl-5H-dibenzo[b,g]-1,4-oxazocine-6-one (prepared as previously described, 190 g, 0.698 mol) in dry MeOH (290 mL) was stirred at room temperature during the addition of powdered potassium hydroxide (15.6 g, 0.28 mol) and the mixture was stirred for 5 min. The mixture was then cooled (cold water bath) during the dropwise addition of methyl iodide (19.7 g, 0.14 mol) and stirring continued for 2 h. The mixture was poured into water and extracted with ether, and the organic layer was washed with 2 N HCl, dried (MgSO₄) and evaporated to give 3-chloro-1,5-dimethyl-5H-dibenzo[b,g]-1,4-oxazocin-6-one: yield 17.5 g (88%); IR (CHBr₃) ν max 1660, 1470 cm⁻¹.

The N-methylxoxacinone (16.0 g, 0.056 mol) was hydrolyzed by using the procedure described in method A. The crude product was chromatographed on silica gel (70-230 mesh ASTM), eluting with ethyl acetate/40-60 °C petroleum followed by crystallization from aqueous ethanol to give 81: yield 2.4 g (14%); mp 174-175 °C. Anal. (C₁₅H₁₄ClNO) C, H, N.

Method B (Scheme II), 2-(2-Amino-6-methylphenoxy)phenyloxenacetic Acid (99). The preparation of 3-[2-(2-chloro-6-nitrophenoxy)phenyl]-prop-1-one was carried out in essentially the same manner as that of 3-[2-(2-chloro-6-nitrophenoxy)phenyl]-2-methylprop-1-one described earlier, using the potassium salt of 2-allylphenol (215 g, 1.25 mol), 2-allylphenol (168 g, 1.25 mol), and 2-chloro-3-nitrotoluene (66.7 g, 0.39 mol). The crude product was distilled under reduced pressure to give pure material: yield 83.6 g (79%); bp 166-168 °C (0.8 mm); IR (thin film) ν max 1640, 1540 cm⁻¹.

The 2-allyl diphenyl ether (17.0 g, 0.063 mol) was dissolved in a mixture of acetic acid (150 mL) and water (20 mL), and potassium permanganate (44 g, 0.28 mol) was added portionwise over 1.5 h at 9-10 °C. The mixture was stirred at room temperature during the addition of sodium periodate (70-230 mesh ASTM) eluting with ethyl acetate, followed by crystallization from aqueous ethanol to give 99: yield 13.0 g (72%). A small sample was further purified by chromatography using silica gel (70-230 mesh ASTM) eluting with ethyl acetate, followed by crystallization from aqueous ethanol to give 99: mp 145-146 °C. Anal. (C₁₅H₁₄O₄) C, H, N.
of the arthritis was assessed by measurement of the volume of the paw. The resulting precipitate was filtered and the filtrate was evaporated to dryness. The resulting oil was dissolved in ethereal HCl and the precipitated hydrochloride salt was filtered off, washed with ether, and then added to aqueous ammonium solution. The aqueous layer was extracted with ether, which was separated, washed with water, dried (MgSO₄), and evaporated to give crude 3-[2-(aminomethyl)-6-methylphenoxymethyl]phenylprop-1-one: yield 11.5 g (93%); IR (thin film) ν max 3420, 1685 cm⁻¹.

A mixture of the amino acid (11.0 g, 0.039 mol) in acetic acid (240 mL) and water (80 mL) was oxidized with potassium permanganate (31.6 g, 0.2 mol) by using the procedure described in method A to give 3-[2-(N-acetamidomethyl)-6-methylphenoxymethyl]phenylprop-1-one: yield 6.9 g (60%); IR (CHBr₃) ν max 3400, 1620, 1490 cm⁻¹.

The acetamidopropene (11.0 g, 0.039 mol) was methylated in acetic acid (240 mL) and water (80 mL) with methyl iodide (26.6 g, 0.19 mol) by using the procedure described in the preparation of the nitro acid 99. The crude product was chromatographed on silica gel (70-230 mesh ASTM), eluting with chloroform, to give 2-[2-methyl-5-(N-methylacetamido)phenyl]prop-1-ene: yield 1.1 g (19%): mp 144-145 °C. Anal. (C₁₆H₁₇N₀₃) C, H, N.

The dihydrogenated at 3 atm at 95-100 °C for 2 h. After cooling, the mixture was filtered and the filtrate was evaporated to give crude 3-[2-(2-amino-6-nitrophenoxy)phenyl]-1-ene (22.7 g, 0.084 mol), iron filings (19.1 g, 0.34 mol), and acetic acid (100 mL) was stirred and heated under reflux for 12 h. The mixture was then filtered to remove ferric salt, washed with water, dried (MgSO₄), and evaporated to dryness and the residue was chromatographed on silica gel (70-230 mesh ASTM), eluting with chloroform, to give 2-[2-methyl-5-(N-methylacetamido)phenyl]prop-1-ene: yield 6.9 g (60%); IR (CHBr₃) ν max 1720, 1640, 1400 cm⁻¹.

A solution of the N-methylacetamidomethyl (11.0 g, 0.037 mol) in acetic acid (240 mL) and water (80 mL) was oxidized with potassium permanganate (31.6 g, 0.2 mol) by using the procedure described in the preparation of the nitro acid 99. The crude product was chromatographed on silica gel (70-230 mesh ASTM), eluting with chloroform, to give 2-[2-methyl-5-(N-methylacetamido)phenyl]prop-1-ene: yield: 6.9 g (60%); IR (CHBr₃) ν max 1720, 1640, 1400 cm⁻¹.

The acetamidopropene (11.0 g, 0.039 mol) was methylated in acetic acid (240 mL) and water (80 mL) with methyl iodide (26.6 g, 0.19 mol) by using the procedure described in method A to give 3-[2-(N-acetamidomethyl)-6-methylphenoxymethyl]phenylprop-1-one: yield 6.9 g (60%); IR (CHBr₃) ν max 3420, 1685 cm⁻¹.

The dihydrogenated at 3 atm at 95-100 °C for 2 h. After cooling, the mixture was filtered and the filtrate was evaporated to give crude 3-[2-(2-amino-6-nitrophenoxy)phenyl]-1-ene described above (22.7 g, 0.084 mol), iron filings (19.1 g, 0.34 mol), and acetic acid (100 mL) was heated under reflux for 12 h. The mixture was then filtered to remove ferric salt, washed with water, dried (MgSO₄), and evaporated to dryness and the residue was chromatographed on silica gel (70-230 mesh ASTM), eluting with chloroform, to give 2-[2-methyl-5-(N-methylacetamido)phenyl]prop-1-ene: yield 11.5 g (93%); IR (CHBr₃) ν max 3400, 1620, 1490 cm⁻¹.
Mineralocorticoid Properties of Potential Metabolites of 18-Hydroxydeoxycorticosterone and 18-Hydroxyprogesterone

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The high secretion rate of 18-hydroxydeoxycorticosterone in hypertensives and the steroids implication as a mineralocorticoid has led to the synthesis of potential di-, tetra-, and hexahydro metabolites of it and 18-hydroxyprogesterone. These potential metabolites have been synthesized by reduction of the double bond and the 3- and 20-ketones, singly or in combination. They have been evaluated for pro- and antimineralocorticoid activity and their affinity for the renal aldosterone receptor. All except one of the potential metabolites either lack or have reduced mineralocorticoid activity and aldosterone receptor binding affinity. The exception is the 3-ketopregn-4-ene-18,20-diol which has high receptor activity but functions as an aldosterone antagonist.

Although inactive as a mineralocorticoid, this metabolite appeared to potentiate the action of aldosterone, although this activity has not been confirmed. Reduced metabolites of 18-OH-DOC have been observed after incubation with the adrenals and liver of adult rats. These metabolites are all tetrahydro derivatives derived from reduction of the A-ring enone, primarily the 3α-hydroxy-5α-pregnane and 3α-hydroxy-5β-pregnane derivatives, although the 3α-hydroxy-5α-pregnane has been tentatively identified. This reduction pattern indicates that the metabolism of 18-OH-DOC is similar to that of progesterone and would be expected to proceed through the saturated 3-ketones. Additionally, the reported isolation of the reduced 20-ketone metabolite of aldosterone indicates that this group is potentially capable of reduction in the 18-OH-DOC series. At the inception of this work, none of the potential dihydro, tetrahydro, and hexahydropotential metabolites had been published. To the best of our knowledge, no published report exists on the biological activity of the metabolites of 18-OH-DOC. As part of our continuing interest in 18-oxygenated steroids, we have prepared a series of di-, tetra-, and hexahydro derivatives of both 18-hydroxyprogesterone (18-OH-PROG, 4E) and 18-OH-DOC and evaluated them for their affinity for the renal aldosterone receptor.

Both oxidized and reduced metabolites of 18-OH-DOC have been isolated. Melby isolated 16,18-dihydroxydeoxycorticosterone from human adrenal incubations.

(4) Peron, F. G. Endocrinology 1961, 60, 39.