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trans-2,3b,4,5,7,8b,9,10-Octahydronaphtho[1,2-*c*:5,6-*c*']dipyrazole, a New Orally Active Antiallergic Compound

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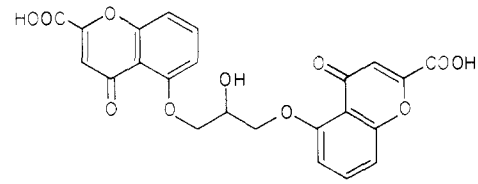
The synthesis and antiallergic activity of a new heterocyclic steroidal molecule are described. Compound 1 was shown to inhibit the rat passive cutaneous anaphylaxis and its activity in this system was compared to that of disodium cromoglycate. It is orally active at a dose of 35 mg/kg (ED_{50}) and its activity persists for up to 6 h for larger doses.

The search for active inhibitors of mediator release in sensitized tissues is a field that has received a great deal of attention since the discovery of disodium cromoglycate (DSCG).[2] Active drugs in this area, of which DSCG is the prototype, do not appear to interfere with antigen–antibody association, but rather they seem to inhibit the process by which such association initiates the release of chemical mediators.[3] Recent cell binding studies carried out with [^{3}H]-DSCG suggest that the site of action of DSCG is at or near the surface of the target cell membrane.[4] Likewise, the reported inhibition of hypersensitivity reactions in humans by the pentapeptide Asp-Ser-Asp-Pro-Arg, which displaced IgE from its binding sites on dermal target cells, suggests that this inhibitor also acts at or near the cell membrane.[5] It seems, therefore, that membrane selectivity is necessary for some substances to behave as inhibitors of anaphylaxis.

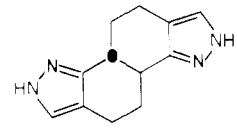
When compound 1 was found to have activity against passive cutaneous anaphylaxis (PCA), it was of interest to consider whether or not its steroid-like structure was in any way responsible for the observed activity. Although steroids do not appear to have a direct effect on the release of mediators of anaphylaxis, they are known to interact with membranes and promote biomembrane stabilization.[6,7] In addition, pyrazoles fused to a steroid A ring are known to enhance their antiinflammatory activity.[8] Another feature of compound 1 worth considering was the symmetric disposition of the pyrazole rings. Symmetry does not appear to be a prerequisite for anti-PCA activity as shown by the fact that there are many active molecules that are nonsymmetric.[9] However, a symmetric molecule may provide some information about the distance between active sites on the receptor even if both functional groups are involved in drug–receptor interactions that may differ in significance.

The synthesis and biological activity of compound 1 are the subject of the present paper.

Chemistry. The synthetic sequence started with commercially available 1,5-decalindiol (**2**, mixture of isomers) which was subjected to oxidation under the conditions reported by Johnson et al.[10] (Scheme I). As reported by the same authors, the resulting dione was equilibrated to its more stable trans isomer and obtained as pure *trans*-decalin-1,5-dione (**3a**). Treatment of **3a** with ethyl formate in pyridine utilizing sodium methoxide as catalyst afforded intermediate **4** which according to NMR appears to be a mixture of rapidly equilibrating tautomers (**4a** and **4b**).[11] NMR spectral comparison with *cis*- and *trans*-decalin-1,5-dione established that compound **4** had the trans configuration.[11] Furthermore, compound **4** was also obtained starting with pure *cis*-decalin-1,5-dione, thus eliminating the need to purify and separate the mixture of diones **3a** and **3b**. Final product **1** was obtained also as a mixture of pyrazole tautomers in good yield from the reaction of **4** with hydrazine in refluxing ethanol. In a similar fashion compounds **5** and **6** were obtained from **4** when treated with methylhydrazine and phenylhydrazine, respectively. According to Cospeau and Elguero,[12] the keto enol equilibria in hydroxymethylene ketones and the two nucleophilic nitrogens of monosubstituted hydrazines could give rise to two isomers. In the case of methylhydrazine the major component of the mixture appeared to be compound **5** which resulted from the attack of the most nucleophilic alkyl nitrogen on the exocyclic carbonyl carbon of compound **4b**. Purification of **5** was accomplished after several recrystallizations from acetone. When phenylhydrazine was employed the nucleophilicity of the nitrogens was reversed and only one product was isolated. Structure **6** is proposed based on previous findings that state that hydroxymethylene ketones cyclize with arylhydrazines to give exclusively the N(1) derivative.[13]



DSCG



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Biological Activity and Discussion. Compound 1 inhibited the passive cutaneous anaphylaxis (PCA) reaction when administered per os 1–6 h before antigen challenge. The characteristics of the inhibitory effect of compound 1 are summarized in Table I. PCA reactions

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Scheme I

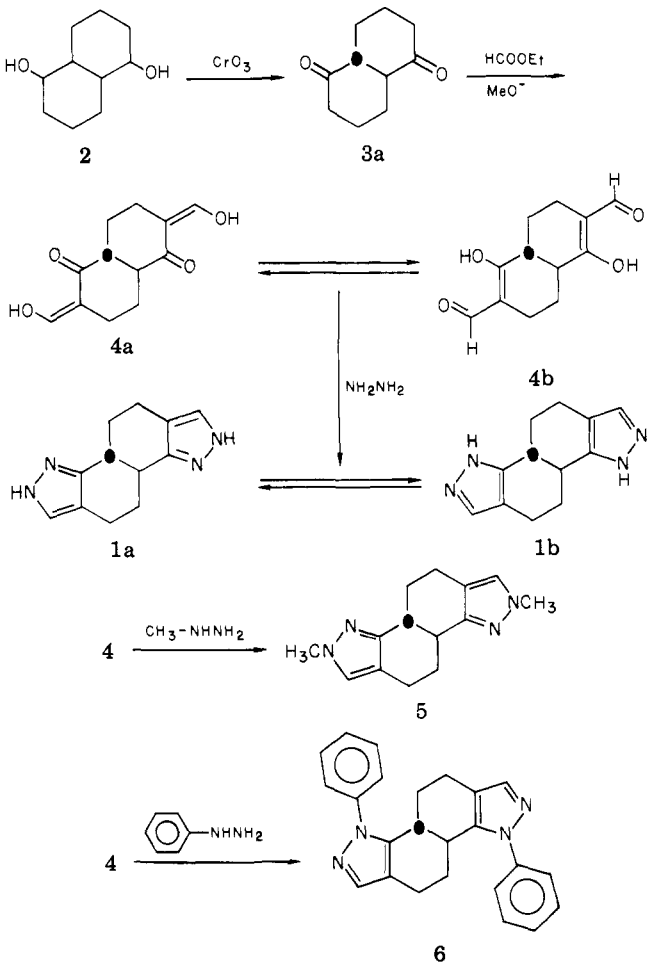

Table I. Percent Inhibition of the Rat Reaginic PCA Induced by Compound 1 per os 1 h before Antigen Challenge

Compd 1, mg/kg	Diameters,[e] mm	p	% inhibn
None	82 ± 14		
25	55 ± 11	n.s.[a]	33
50	32 ± 16	0.01	61
100[b]	29 ± 19	0.01	65
200[c]	30 ± 16	0.01	63
DSCG[d]	18 ± 13	0.01	78

[a] Not significant. [b] Percent inhibition at this dose level after 3 h was 67%. [c] Percent inhibition at this dose level after 6 h was 52%. [d] 0.5 mg/kg iv, administered simultaneously with the antigen. [e] Sum of diameters of reactions at four antibody sites.

in the rat were induced with mouse antiserum. The use of heterologous species to measure mouse reaginic antibodies has been documented.[14] The 50% inhibitory dose (ED_{50}) was 35 mg/kg (visual observation) for compound 1 administered 1 h before antigen. Doses five to six times the ED_{50} did not markedly enhance inhibition; this seemed to plateau at 60–65% inhibition which was only surpassed by giving repeated doses. The larger single doses, however, increased substantially the duration of the inhibitory effect.

Compound 1 did not inhibit skin reactions due to histamine or other chemical mediators released from mast cells by compound 48/80,[15] and all available evidence suggests that it inhibits the release of histamine from tissue mast cells as postulated for DSCG. The latter drug, however, is active only when administered intravenously or intraperitoneally, while compound 1 is active when given per os. The effect of predosing and the duration of action also differs for the two compounds. In rats treated with DSCG there is a loss of inhibition by predoses that induced 63 and 75% inhibition.[16] In contrast, in rats treated with compound 1, increased inhibition is produced by predoses in excess of the ED_{50}. Independently of the dose, the effect of DSCG given iv is rather transient and it is detectable only during a 0–15-min period.[17] The effect of compound 1 is seen 30 min after ingestion and persists for as long as 6 h depending on the dose given. In addition, predosing with compound 1 also was found to increase the anti-PCA activity of DSCG given iv.

Both hydrogens on the pyrazole rings of compound 1 appear to be important for activity. Although no analogue with only one free hydrogen on one of the pyrazole rings was prepared, other nonsymmetrical structures tested in our laboratories which contain only one unsubstituted pyrazole ring are found to be less active than 1.[18] Activity is lost by their replacement with either methyl or phenyl groups as in compounds 5 and 6. Compounds 5 and 6, as well as the precursor of the series (compound 4), were found to be inactive at 100 mg/kg po. Although compound 4 appeared to have met the structural requirements for binding to the receptor in the same fashion as compound 1, activity was totally lacking. Possibly, this is a consequence of an inadequate transport to the active site. In order to solve this question attempts were made to test compound 4 by the iv route, but it proved to be quite insoluble and its disodium salt required an exceedingly high pH to be maintained in solution, hampering the use of the iv route.

Whether or not DSCG and compound 1 interact with the same receptor on the cell's surface is not yet known. If similarities are considered, it is tempting to think that each compound may intereact through hydrogen bonding with specific receptor structures through either the ether and hydroxyl radicals of DSCG or the pyrazole rings of compound 1. However, the expected differences in pK_a values for these two compounds will definitely make DSCG more hydrophilic and compound 1 more hydrophobic. If hydrophobicity is in any way important for these drugs to intereact with the target membrane, compound 1 should be partitioned more favorably than DSCG due to its hydrophobic backbone and higher pK_a. This difference may in part explain the transient effect of DSCG and the long-lasting effects observed for compound 1. If dissimilarities are stressed, then the lack of desensitization observed for compound 1 as opposed to DSCG may suggest a different mechanism of action at another level.

Experimental Section

General. All chemical reagents are commercially available. They were purchased either from E. Merck or Aldrich Chemical Co. Melting points were determined by means of an Electrothermal capillary melting point apparatus, and they are uncorrected. A Perkin-Elmer Model 727 infrared spectrophotometer was employed for IR spectra, using Nujol mulls. A Varian Associates Model EM-360 analytical NMR spectrometer was used for NMR spectra of either deuteriochloroform or Me_2SO-d_6 solutions with internal tetramethylsilane (δ 0.00) at ambient temperature. Mass spectra were obtained in a Hitachi Perkin-Elmer RMU-6H instrument at 70 eV. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. All compounds gave analytical results for C, H, and N within ±0.04% of the theoretical values.

Biological Method. Reaginic serum specific for the dinitrophenyl determinant (DNP) was obtained in mice immunized with dinitrophenylated bovine γ-globulin ($DNP_{31}BCG$) in alumina gel.[19] The PCA test was performed in rats.[20] Sprague–Dawley rats that weighed 100 g were injected with 0.1-mL serum dilutions

at six intradermal sites and challenged iv 48–72 h later with 1 mg of dinitrophenylated human serum albumin ($DNP_{35}HSA$) plus 2 mg of Evans blue in 0.2 mL of 0.15 N NaCl. Thirty minutes after challenge the animals were sacrificed and the diameter of the skin reactions was measured on the inverted skin. Percent inhibition was calculated with the formula, $\% = 100(1 - a/b)$, where a is the sum or the reaction diameters in the treated animals and b the sum of the reaction diameters in the control animals.[21] Each variable was tested in groups of five rats.

***trans*-2,3b,4,5,7,8b,9,10-Octahydronaphtho[1,2-*c*:5,6-*c*']-dipyrazole (1).** A mixture of 1.11 g (5 mmol) of 4,[11] 1 mL (ca. 0.02 mol) of hydrazine hydrate, and 50 mL of ethanol was refluxed for 6 h. After the total volume was reduced to about one-half, the compound slowly precipitated at room temperature. The solid was collected, dried, and recrystallized twice from ethanol to yield 0.7 g (65%) of 1 as very fine off-white crystals: mp 300 °C dec; IR (Nujol) 3200 (s, br), 1600 (w), 1580 (w), 1340 (m), 1180 (m), 1100 (m), 1080 (m), 980 (s), 880 (m), and 820 cm^{-1} (m); NMR (Me_2SO-d_6) δ 7.40 and 7.30 (s's, 2), and 12.6 (br s, 2); mass spectrum m/e 214 ($M^{+}\cdot$). Anal. ($C_{12}H_{14}N_4$) C, H, N.

***trans*-2,7-Dimethyl-3b,4,5,8b,9,10-hexahydronaphtho-[1,2-*c*:5,6-*c*']dipyrazole (5).** This compound was prepared in 31% yield following an identical procedure as for compound 1. Recrystallization from acetone afforded **5** as small white crystals: mp 231–232 °C; IR (Nujol) 1600 (w), 1560 (m), 1300 (m), 1250 (m), 1160 (s), 1020 (w), 1000 (w), 950 (m), 880 (m), 840 (s), and 720 cm^{-1} (m); NMR ($CDCl_3$) δ 2.80 (m, 10), 3.90 (s, 6), and 7.20 (s, 2); mass spectrum m/e 242 ($M^{+}\cdot$). Anal. ($C_{14}H_{18}N_4$) C, H, N.

***trans*-3,8-Diphenyl-3b,4,5,8b,9,10-hexahydronaphtho-[1,2-*c*:5,6-*c*']dipyrazole (6).** This compound was prepared in 26% yield by a similar procedure as for 1 and **5**. Recrystallization from acetone afforded **6** as yellow needles: mp 275–276 °C dec; IR (Nujol) 1600 (m), 1580 (m), 1500 (s), 1050 (m), 960 (m), 770 (m), and 700 cm^{-1} (m); NMR (CF_3COOH) δ 3.00 (br m, 10), 7170 (s, 10), and 8.00 (s, 2); mass spectrum m/e 366 ($M^{+}\cdot$). Anal. ($C_{24}H_{22}N_4$) C, H, N.

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Neuroleptics Related to Butaclamol. Synthesis and Some Psychopharmacological Effects of a Series of 3-Aryl Analogues

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The synthesis and some pharmacological effects of 16 3-aryl analogues of butaclamol, a new antipsychotic drug, are described. The animal models were predictive of neuroleptic activity as well as side effects commonly associated with neuroleptic therapy. The results indicate that the 3-substituent plays a critical role with regard to the potency of the compounds as well as to their tendencies to induce extrapyramidal side effects and/or hypotension.

The synthesis of 3-substituted benzo[6,7]cyclohepta-[1,2,3-*de*]pyrido[2,1-*a*]isoquinolin-3-ol derivatives[1] has led to the emergence of a chemically novel class of neuroleptic agents of which butaclamol,[2,3] the 3-*tert*-butyl derivative, is the most interesting member. Clinical studies[4–8] have established that butaclamol is a potent antipsychotic drug which is devoid of side effects arising from interference with the autonomic nervous system but which induces extrapyramidal side effects.

In the present study, the synthesis of a series of 15 3-aryl analogues of butaclamol is described. These derivatives as well as the previously described 3-phenyl analogue[1] were evaluated in animal models which are either indicative of the relative potencies of these compounds as neuroleptic agents or are predictive of their tendency to induce extrapyramidal side effects and hypotension. The compounds were compared to butaclamol.

Chemistry. The 3-aryl analogues studied comprised

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