particle counter (Coulter Electronics, Inc., Hialeah, FL).

The L-1210 cells do not adhere to the culture dish and can be separated from one another by aspirating the culture through the tip of a pipet. Thus dispersed, the cells were suspended in a total volume of 10 mL with a balanced salts solution (Isoton, Coulter Diagnostics, Hialeah, FL) and counted. The B16 cells do attach to the plastic culture surface. The medium was removed from these cultures, and 0.2 mL of 0.01% crystalline porcine trypsin, 0.1% EDTA in divalent cation-free phosphate-buffered saline was added to each well. After 5 min at 37 °C, the culture plates were chilled on ice and 0.1 mL of phosphate-buffered saline was added to each well. The number of cells in the suspensions was then determined. The number of cells per well was plotted as a function of the concentration of the test agent, and the dose that reduced the cell count to 50% of the untreated controls was determined and is reported as the ID_{50}.

The IC_{50} (μg/mL) values for P388 (mouse leukemia, 9PS) and 9KB (human epidermoid carcinoma of the nasopharynx) cytotoxic cell culture activity were determined by following the established protocols of the National Institutes of Health, National Cancer Institute,[78] at the Purdue Cancer Center Cell Culture Laboratory. The KB cell line, derived from a human epidermoid carcinoma (KB-ADL; oral cavity), was supplied by the NCI contractor. The cell culture screen was performed according to the standard protocol.[78] Samples were dissolved in dimethyl sulfoxide before final dilutions to 100, 10, 0.1, 0.01, 0.001 μg/mL in the growth medium. Samples were run in duplicate. The ID_{50} is the dose of sample that inhibits cell growth to 50% of the untreated control values. The ID_{50} values were obtained by extrapolation from the least-squares fit of the dose-response curve. The PS cell line, derived from a mouse lymphocytic leukemia (P388; spleen and lymph nodes), was supplied by the NCI contractor. The cell culture screen was performed as described above.

Each IC_{50} determination was run in duplicate and was repeated with samples **1a**, **1b**, **5a**, **5b**, and **7-10**. The IC_{50} values (<±10%, unless otherwise noted) are detailed in Table I.

Acknowledgment. This work was assisted financially by the National Institutes of Health (CA 42056, AI 13155, ES 03651) and the Alfred P. Sloan Foundation. We thank Sharon M. Rinzel and Carol Katerjohn of Eli Lilly and Co. for performing the in vitro CCRF-CEM cell culture assays and the in vivo 6C3HED lymphosarcoma testing and Dr. Homer Pearce for his assistance.

Supplementary Material Available: A table summarizing the results of the complete series of agents evaluated for in vitro antimicrobial and cytotoxic activity (46 compounds), experimental details for the in vitro CCRF-CEM (human lymphoblastic leukemia) cell culture assay, and experimental protocols for the in vivo 6C3HED lymphosarcoma testing (7 pages). Ordering information is given on any current masthead page.

Notes

The Dopaminergic Moiety of the Ergots: A Controversial Topic Studied with Molecular Mechanics

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Conformational analyses of the side chain of model compounds of the in vivo active dopamine receptor agonist 4-[2-(di-*n*-propylamino)ethyl]indole (DPAI) were performed with molecular mechanics calculations. The results from these calculations, together with the possibility of meta hydroxylation of indoles in vivo, led to the proposal of fitting 6-hydroxy-4-[2-(di-*n*-propylamino)ethyl]indole (6-OH-DPAI), (*S*)-5-hydroxy-*N*,*N*-dialkyl-6,7,8,9-tetrahydro-3*H*-benzo[*e*]indol-8-ylamines and (*S*)-5-hydroxy-2-(dialkylamino)tetralins in a common concept, considering both stereochemistry and hydrogen-bond function in such an overlap. This study emphasizes the importance of considering both conformational analysis and the possibilities of metabolic activation when performing structure–activity studies based on flexible compounds and in vivo data. The answer to the question as to which part of the ergot molecule is responsible for its dopaminergic effect is thus ambiguous. It is possible that the pyrrolylethylamine moiety of the ergots contributes to both in vitro and in vivo effects, and that their 13-OH metabolites contribute, possibly significantly, to their in vivo effects.

The beneficial clinical effects of bromocriptine in the treatment of Parkinson's disease have prompted many attempts to deduce which part of the ergoline structure (1) is responsible for its dopamine (DA) receptor agonist effects.[1-4] The most thorough work has been performed by Kornfeld et al.,[5-8] and these authors conclude that it is the pyrrolylethylamine moiety that is the DA pharmacophore. They also emphasize the importance of stereochemical congruence between different structural classes of DA agonists, and they present data on several pyrrole, pyrazole, and other heterocyclic analogues that support their ideas.[9] Basically, the 5*R* absolute configuration of the ergolines (1) and the 6a*R* absolute configuration of apomorphine (2) superimpose, and hydrogen-bond donors are the pyrrole NH and the 11 phenol OH in the ergolines

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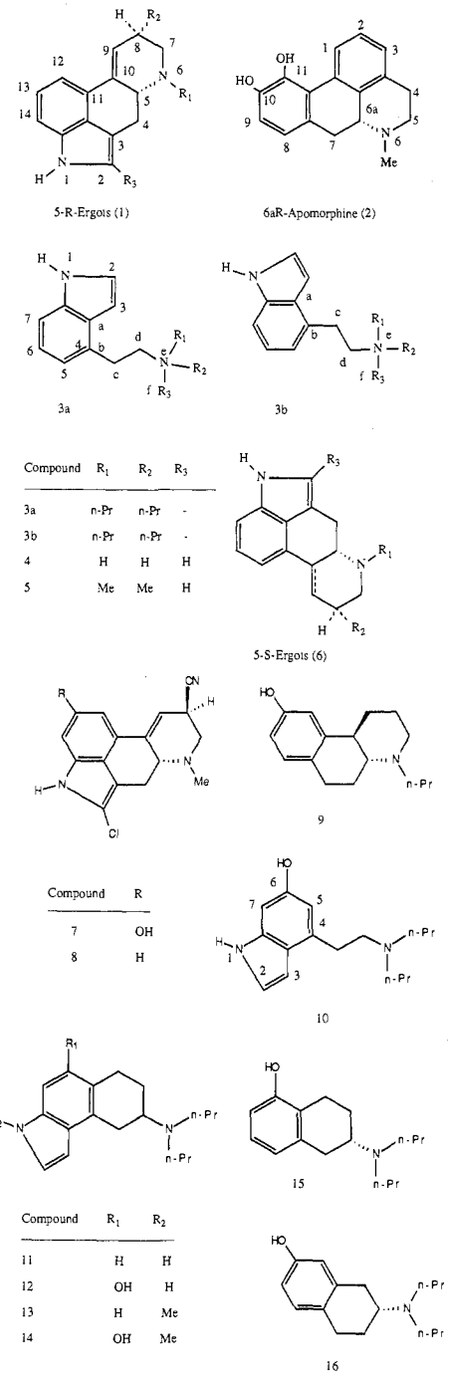
Scheme I



and apomorphine, respectively (see Scheme I).

Other research groups have focused upon the phenethylamine moiety in their search for the dopaminergic moiety of the ergots.[1,2,10,11] Cannon et al. presented 4-

Table I. Local Minima Emanating from the Two Angle Driver on Compound 4

conf	τ_1 = a–b–c–d[a]	τ_2 = b–c–d–e[a]	steric energy, kcal/mol	distance, Å: N(basic)–N(pyrrole)	distance, Å: N(basic)–arom ring plane
4A	80	50	3.22	5.47	2.31
4B	274	50	1.77	4.50	−2.13
4C	81	180	5.90	6.65	1.31
4D	279	180	5.90	6.65	−1.32
4E	86	309	1.77	4.50	2.13
4F	281	310	3.22	5.47	−2.31
4G	1	180	9.19	6.67	0.03
4H	180	180	6.87	7.18	−0.01

[a] The torsion angles denoted with the letters a–e refer to compound 4 in Scheme I.

[2-(di-*n*-propylamino)ethyl]indole (DPAI (**3**)) as such a candidate.[10,11] In their view, the phenethylamine portion and the pyrrole NH of the ergots (**1**) serve the same functions as the phenethylamine portion and the meta phenol OH in i.a. apomorphine (**2**), respectively. These authors did not address the stereochemical aspect of the problem, probably because the compound studied is nonchiral. However, superposition of the 2-aminotetralin moieties of the natural (*R*)-ergolines (**1**) and 6a(*R*)-apomorphine (**2**) is not possible from the stereochemical point of view. Instead, the corresponding moieties of the unnatural (*S*)-ergolines (**6**) and 6a(*R*)-apomorphine (**2**) are perfectly superimposable, placing the pyrrole nitrogen in **6** and the 11-OH group in **2** at the same position.[12] The (*S*)-ergolines have been reported to be inactive in previous studies.[13] One possible reason for this might be the steric impact of the 8-substituent present in these structures, and it has been proposed by Wikström et al. that the (*S*)-ergolines (**6**) might be active dopaminergic agents if this 8-substituent is removed.[12] Thus, the possibility remains that DPAI (**3**) really could represent a dopaminergic moiety, however, not of the natural *R*- (**1**) but rather of the unnatural (*S*)-ergolines (**6**).

The conformation of the ethylamine side chain in DPAI might play a crucial role in this reasoning and should be considered before any relevant comparisons between this flexible compound and the semirigid ergolines can be performed. In the conformation mimicking the (*S*)-ergolines (conformation **3a**) there is a "pentane interaction",[14-17] which might indicate higher steric energy for this conformation than for the other possible rotameric forms (i.e., conformation **3b**). Conformation **3a** corresponds to the α rotamer of DA, and it was suggested by Cannon,[11] based on conformational studies with Dreiding models, that the corresponding β rotamer should be the energetically preferred one. Despite these qualitative conformational aspects, Cannon suggested that the α rotamer of DPAI would be the DA pharmacophore of the ergots (**1**).[11]

In order to investigate this problem we performed molecular mechanics conformational calculations on the ethylamine side chain of the model compounds **4** and **5** in

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Table II. Conformations **5G–5H** Emanating from Conformations **4G–4H** and with All Three Staggered Conformations of the *N,N*-Dimethylammonium Group Included

conf	τ_1 = a–b–c–d[a]	τ_2 = b–c–d–e[a]	τ_3 = c–d–e–f[a]	steric energy, kcal/mol	distance, Å: N(basic)–N(pyrrole)	distance, Å: N(basic)–arom ring plane
5G1	280	190	56	9.08	6.76	−1.46
5G2	3	178	179	13.93	6.69	0.12
5G3	80	170	304	9.08	6.76	1.46
5H1	170	191	56	10.24	7.23	0.47
5H2	181	179	179	11.41	7.31	-0.06
5H3	190	170	304	10.24	7.23	−0.47

[a] The torsion angles denoted with the letters a–f refer to compound **5** in Scheme I.

their protonated forms, using the two angle driver option in the MM2 program[18] for compound **4** to screen out local minima. The two angles driven were τ_1 = a–b–c–d (see Table I) and τ_2 = b–c–d–e (see Table I), and both angles were driven 0–360° with an increment of 20°. Local minimum conformations found were then subjected to full minimization with MM2. Since all potent dopaminergic agonists so far studied are fairly planar in their overall structure, and since the basic nitrogens in these structures are always close to the plane of the aromatic ring (0–1.2 Å), the pharmacologically active conformation of DPAI should also have its basic nitrogen close to that plane.[19] This leaves two fully extended conformations of this compound possible, i.e., **3a** and **3b**, which were also included in the calculations. These two conformations of compound **4** (Table I) were used to build the corresponding starting geometries of the dimethylated analogue **5**. All three possible staggered starting conformations of the dimethylammonium group were built with an option in the MM2 program by substituting two at a time of the ammonium hydrogens for carbon and then adding three hydrogens to those carbon atoms. These different conformations of **5** were then subjected to full minimizations with MM2 (Table II).

Ergot metabolism is a complicated matter, but it has been shown that aromatic hydroxylation in a position meta to the indole nitrogen is a prominent pathway, i.e., leading to the 13-hydroxy ergots. Parli et al.[20] showed that 13-hydroxylergotrile (**7**) is more potent than lergotrile (**8**) itself, and Wikström et al.[12] emphasized the structural and stereochemical similarity between the 13-hydroxyergolines and the very potent DA receptor agonist *trans*-(4a*R*,10b*R*)-9-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (*trans*-(4a*R*,10b*R*)-9-OH-4-*n*-Pr-OHBQ (**9**)).

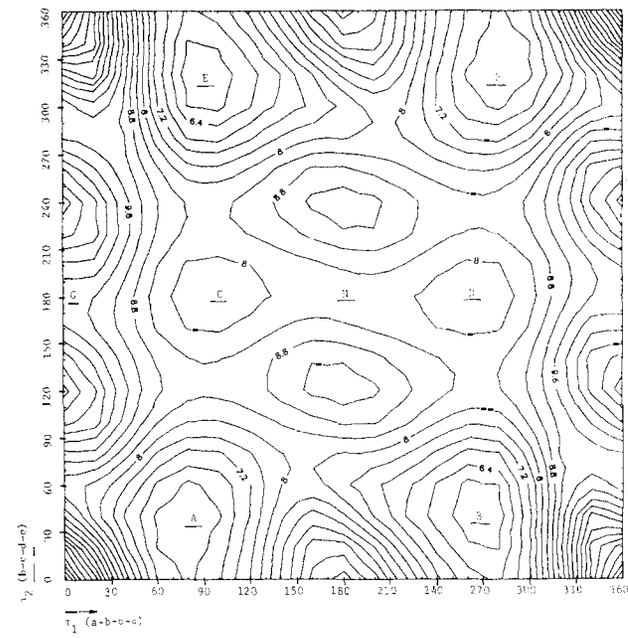

Figure 1. Topographical plot for the two angle driver on compound **4**.

In the first publication on DPAI it was implied that this compound might have to be bioactivated before excerting its effect.[10] Consequently, the same authors later showed that 6-OH-DPAI (**10**) really is more active than DPAI itself, and in addition, it is active in vitro and has no lag period before excerting its effect in vivo, which is the case with DPAI.[21] This very interesting finding is fully in concert with the previously discussed metabolic activation, i.e., the 13-hydroxylation of the ergots. By the introduction of the 6-OH function, one has the option of regarding this phenolic hydroxyl group as being the hydrogen bond donor function when looking for the dopaminergic moiety in compound **10**.

Another very recently published class of indole-containing, dopaminergic compounds is the *N,N*-dialkyl-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-ylamines (e.g., **11**).[22] These compounds have been tested in three different in vivo models, but no information is available on the obvious possibility of bioactivation via aromatic meta hydroxylation. In analogy to the ergots and DPAI, such an hydroxylation should lead to the 5-OH analogue (**12**), which can be considered to be an analogue of the very potent DA receptor agonist 5-hydroxy-2-(di-*n*-propylamino)tetralin (5-OH-DPAT; **15**).[12] Compound **11** was not resolved, but

(18) Allinger, N. L.; Yuh, Y. *Quantum Chemistry Program Exchange* **1980**, program *13*, 395. The MM2 program (MM2-85, available from the Quantum Chemistry Program Exchange and from Molecular Design, Ltd.) has been modified (R. Kok, unpublished) to calculate hydrogen bonds. The hydrogen-bond term has the same functional form as a van der Waals interaction, and we have adjusted these parameters to reproduce the energies obtained from several ab initio calculations and electron-diffraction results on compounds that hydrogen bond either with another molecule or internally. Of particular interest here are the ammonium hydrogen (type 28) to phenol oxygen (type 6) or aromatic carbon (type 2) interactions, which have the hydrogen bond parameters: VdW constant ϵ = 2.200 kcal and sum of VdW radii = 2.080 Å, and VdW constant ϵ = 1.000 kcal and sum of VdW radii = 2.180 Å, respectively. Of course, the dipole–dipole interactions inherent in MM2 are still included in the calculations separate from the new H-bond parameters.

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(22) Asselin, A. A.; Humber, L. G.; Voith, K.; Metcalf, G. *J. Med. Chem.* **1986**, *29*, 648.

it was suggested that the active enantiomer should have the *R* configuration.[22]

MM2 Calculations and Superpositions. All calculations were performed on a Digital Microvax Workstation II, using the MM2 programs.[18] Starting geometries were created with the Model graphics input.[23] Locally developed graphics software was used for molecular display, fit, and data extraction.[24]

Results and Discussion

The results from the MM2 calculations on the model compound **4** with the two angle driver option are presented as a topographic plot in Figure 1. The six obvious local minimum conformations (A–F) identified for compound **4** were used as starting geometries in full minimizations, and the results from these calculations are given in Table I. As seen from this table and Figure 2, the global minima (B and E, two due to symmetry) have the ethylamine side chain in a gauche conformation, essentially perpendicular to the aromatic ring plane and bending back toward the aromatic ring system. The results from the calculations show that the major reason for this stability is hydrogen bonding between the ammonium hydrogens and the aromatic carbon atoms. The two largest contributions to these stabilizing effects for conformations B and E come from the interactions (in MM2-85, attractive VdW interactions[18]) between C3a and C4 and the closest ammonium hydrogen, amounting to 1.17 and 1.12 kcal/mol, respectively.

The three conformations with $\tau_1 = 0°$, $\tau_2 = 60°$ and $\tau_1 = 0°$, $\tau_2 = 180°$ (conformation **4G**), and $\tau_1 = 0°$, $\tau_2 = 300°$ were subjected to full minimizations in order to check if any of them represents a local minimum or not. The results show that only conformation **4G** is a true minimum conformation. This was further substantiated in another minimization, starting from $\tau_1 = 2°$, $\tau_2 = 182°$, which led to the same minimum conformation **4G**. On the contrary, the other two test cases changed their side-chain conformations considerably and finally ended up in conformations **4A** and **4F**, respectively. In addition, the true minimum character of conformation **4H** was double checked by starting a minimization at $\tau_1 = 182°$, $\tau_2 = 182°$. This calculation gave conformation **4H** as the final result.

As stated in the introduction, most potent dopaminergic compounds have their basic nitrogen close to the aromatic ring system carrying the hydrogen bonding donor function (here OH or NH). Apomorphine contitutes an exception to this rule, having its nitrogen 1.2 Å from that aromatic ring.[19] There are only two stable conformations (**4G** and **4H**) that satisfy the requirement of having the basic nitrogen that close to the aromatic ring plane (Table I). These two different conformations of compound **4** were used to create input structures of the other model compound, **5**, and the results from the calculations on **5** are presented in Table II and Figure 3. Interestingly, only one ($\tau_1 = 0°$, $\tau_2 = 180°$) of the three original starting geometries of conformation **5G** represents a local minimum conformation. The other two starting geometries change their side-chain conformations considerably and end up in conformations similar to those of **4C** and **4D**, respectively; i.e., the side chain moves to a perpendicular, instead of a coplanar (with the aromatic system), conformation. Thus, the previously proposed dopaminergic moiety of the ergots, i.e., DPAI conformation **3a**, for which conformation $\mathbf{5G}_2$ (13.9 kcal/mol) constitutes a model, is energetically disfavored as compared to the other fully extended conformation **3b**, here mimicked by conformation $\mathbf{5H}_1$ or $\mathbf{5H}_3$ (10.2 kcal/mol).

Data published on DPAI and its 6-OH metabolite (**10**) support the idea of metabolic activation.[10,21] Taking the conformational analysis data into account suggests that the active conformation of compound **10** (see Scheme I) fits on top of (*S*)-**15** and the superposition of their *N*,*N*-dimethyl analogues is shown in Figure 4a. The superpositions were performed simply by orienting the respective phenyl rings in identical ways in the *xy* plane.

The superposition in Figure 4a leads naturally to the next class of dopaminergic indole compounds, namely, the tetrahydro-3*H*-benz[*e*]indol-8-ylamines (e.g., **11**). As mentioned above, compound **11** is dopaminergically active in three in vivo models and no in vitro data are presented.[22] There is one piece of data in the paper presenting these compounds that indicates that bioactivation could be essential, and that is the fact that oral administration of the *N*,*N*-dimethyl analogue of compound **11** is slightly more efficient than subcutaneous administration. On the basis of a previously published DA receptor model, built on i.a. (+)-butaclamol,[25] the authors predicted that the active enantiomer of compound **11** has the *R* absolute configuration. However, if metabolic activation of **11** to its 5-OH analogue **12** takes place, the active enantiomer of compound **12** should have the *S* and not the *R* absolute configuration. This prediction emanates from the close structural relationship between compounds (*S*)-**12** and (*S*)-**15**, as illustrated with the superposition of their *N*,*N*-dimethyl analogues in Figure 4b.

The authors also emphasized the directionalities of the phenol O–H vs. the pyrrole N–H bond in compounds **11** and **16**, respectively.[22] If active per se, the pyrrole N–H must serve as the hydrogen bond donor function, and since this group has only one defined N–H bond direction, it is more informative as compared to a phenol, which could have two possible O–H directions in the plane of the aromatic ring.

The same paper also deals with the pyrrole N-methylated analogues (cf. **13**).[22] Interestingly, compound **13** is about half as effective as is compound **11** in reversing reserpine-induced catalepsy in mice. If hydrogen-bond donation is a prerequisite for compounds with dopaminergic properties,[12] it follows that compound **13** should be inactive per se. However, its 5-OH metabolite **14** could still have agonistic properties, again with the phenol taking the role of a hydrogen bond donor function. The steric bulk of the pyrrole *N*-methyl group, provided this group is not metabolically cleaved off,[26,27] can possibly be reasonably well accommodated at the drug–receptor interaction.

In a very preliminary study of the potential metabolic hydroxylation of the *N*,*N*-dimethylamino analogue of compound **11**,[28] we administered SKF525A (50 mg/kg ip 30 min before the test compound), which inhibits the oxidative liver enzyme cytochrome P450, to rats ($n = 4$) pretreated with reserpine (5 mg/kg sc 18 h before the test compound). The test compound (1 μmol/kg sc) was administered and the motor activity and the biochemical

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(27) Marko, M. *Eur. J. Pharmacol.* **1984**, *101*, 263.
(28) The *N*,*N*-dimethyl analogue of compound **11** was kindly provided by Dr. L. G. Humber at Ayerst Laboratories.

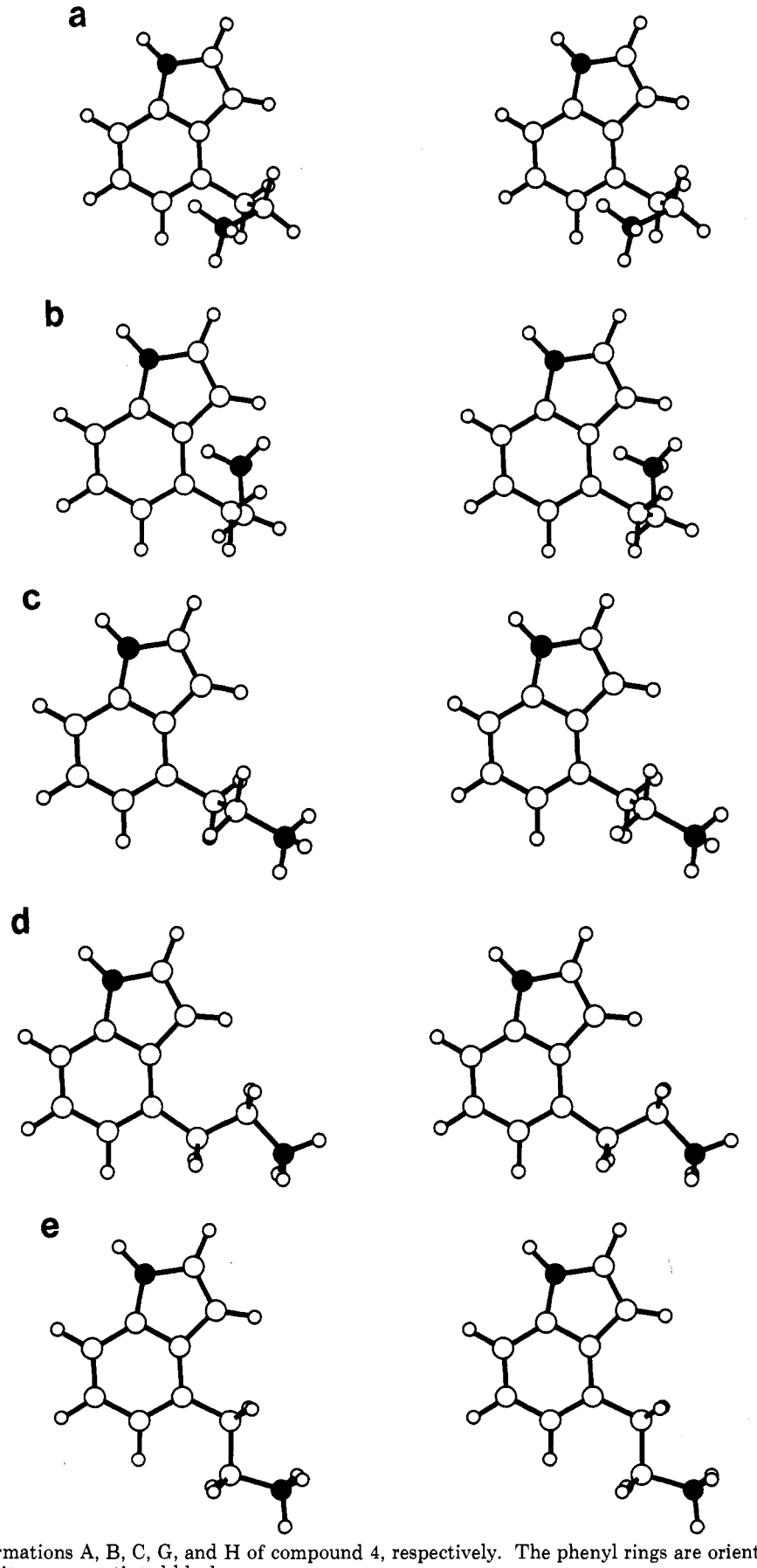

Figure 2. (a–e) Conformations A, B, C, G, and H of compound 4, respectively. The phenyl rings are oriented in the same way in the *xy*-plane, and the nitrogens are tinted black.

effects were measured in accordance to our screening system.[12] The results show that the motor activity response at that dose is blocked, as compared to the control situation without SKF525A. However, the biochemical results are very similar in the two test cases, indicating that aromatic hydroxylation might not be necessary for these

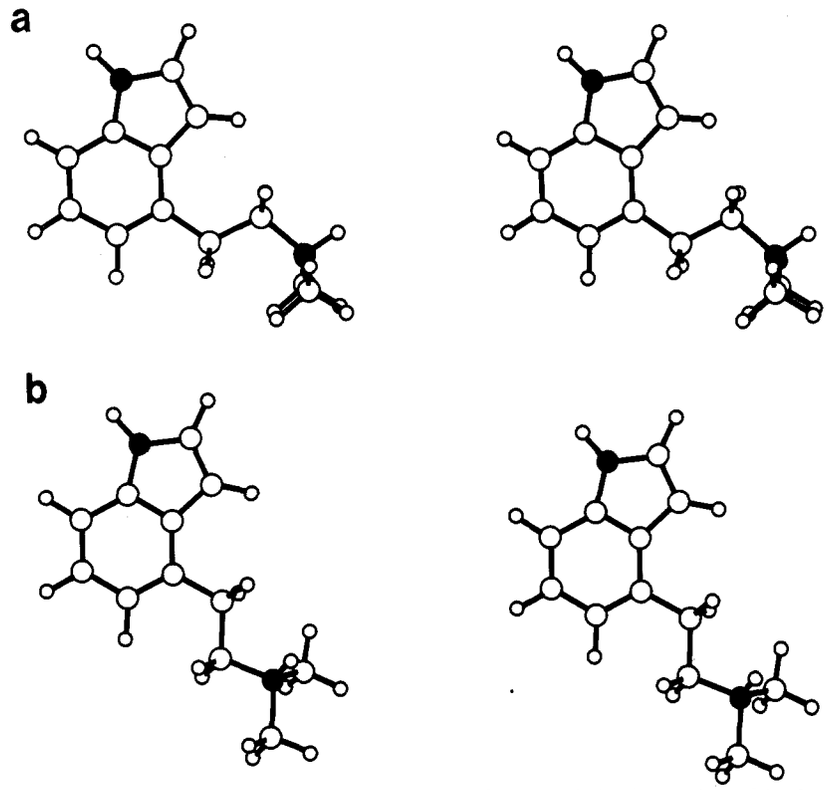

Figure 3. (a, b) Conformations G2 and H1 of compound **5**, respectively. The phenyl rings are oriented in the same way in the *xy*-plane, and the nitrogens are tinted black.

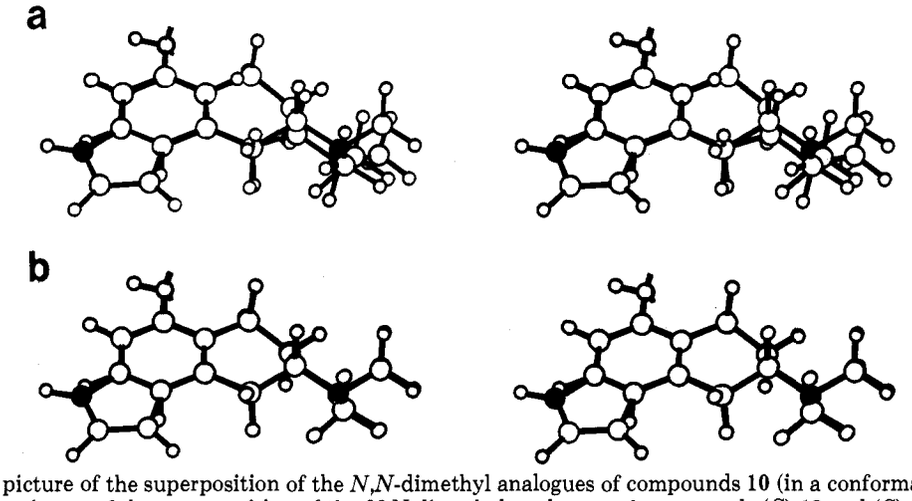

Figure 4. (a) Stereo picture of the superposition of the *N,N*-dimethyl analogues of compounds **10** (in a conformation similar to **5H1**) and (*S*)-**15**. (b) Stereo picture of the superposition of the *N,N*-dimethyl analogues of compounds (*S*)-**12** and (*S*)-**15**. The phenyl rings are oriented in the same way, 45° from the *xy*-plane, and nitrogens are tinted black.

indolamines to exhibit their dopaminergic effects. More thorough studies are needed before any definite conclusions can be drawn.

In conclusion, the present study emphasizes the importance of considering conformational analysis when dealing with flexible structures in medicinal chemistry. In addition, it emphasizes that it is very important to be aware of the possibility of metabolic activation when interpreting in vivo pharmacological data. By taking these two aspects into account, we were able to show that 6-OH-DPAI (**10**) in an extended, stable conformation fits well upon both (*S*)-5-OH-DPAT ((*S*)-**13**) and (*S*)-5-hydroxy-*N,N*-dialkyl-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-ylamines (cf. (*S*)-**12**). We suggest that such a possibility might be a relevant explanation for the in vivo dopaminergic effects demonstrated by these indolylamines.

The question whether it is the phenethylamine or the pyrrolylethylamine moiety that constitutes the dopaminergic pharmacophore of the ergots might thus be ambiguous. When considered from a point of view of per se activity, the answer would be that it is the pyrrolylethylamino portion that is responsible for the dopaminergic effects of the ergots. However, if metabolic meta hydroxylation, which most likely occurs in vivo, is taken into account, the phenethylamine portion could contribute significantly to those effects. The resolution and pharmacological evaluation in vivo as well as in vitro (D2 binding) of the enantiomers of compound **11**, or its analogues, would be crucial for further testing of these speculations. In addition, when these questions have been answered, it should be possible, with computer modeling techniques, to utilize the dopaminergic indole compounds for defining a relative position of a hydrogen bond acceptor site in a DA-receptor model built from many different agonist structures. However, if considering the DA receptor as being dynamic[19] and not static,[29] such a definition

would more have the character of a hydrogen-bond direction than a specifically defined fixed point.

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Registry No. **3a**, 76149-15-0; **4**, 16176-73-1; **5**, 84401-01-4; **10**, 94270-93-6; **10** (*N,N*-dimethyl analog), 109333-99-5; **11** (*N,N*-dimethyl analog), 83343-46-8; **12**-(*S*), 109333-98-4; **13**-(*S*), 109333-97-3; **15**, 68643-08-3.

Resolution, Absolute Configuration, and Cholinergic Enantioselectivity of (-)- and (+)-*c*-2-Methyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane *t*-3-Oxide Methiodide and Related Sulfones[1]

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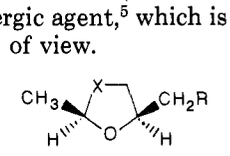
As a continuation of previous studies on chiral cholinergic agonists carrying a 1,3-oxathiolane nucleus, the enantiomers of c-2-methyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane *t*-3-oxide methiodide ((+)- and (-)-**1**) and of *cis*-2-methyl-5-[(dimethylamino)methyl]-1,3-oxathiolane 3,3-dioxide ((+)- and (-)-**2**) were obtained and their absolute configurations established by synthesis. The cholinergic potency of the four isomers was evaluated in vitro on guinea pig ileum and frog rectus abdominis models, and the results show that (-)-**1**, which has the same absolute configuration as L-(+)-muscarine, is a selective and potent muscarinic agent. The (+)-**1** enantiomer is some hundred times less potent than (-)-**1** on the muscarinic guinea pig ileum while, on the same tissue, the corresponding sulfone derivatives ((+)- and (-)-**2**) show no enantioselectivity.

As a continuation of our research on the molecular requirements of the cholinergic receptor recognition site,[2,3] we have recently started the synthesis and study of chiral compounds carrying a 1,3-oxathiolane nucleus. In particular, we have already studied the enantioselectivity of (+)- and (-)-*cis*-2-methyl-5-[(dimethylamino)methyl]-1,3-oxathiolane methiodide (*cis*-oxathiolane).[4] The oxidation product *c*-2-methyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane *t*-3-oxide methiodide (oxathiolane sulfoxide, (±)-**1**) is a potent cholinergic agent,[5] which is rather interesting from many points of view.



(±)-**1**: X = S→O; R = $^{+}N(CH_3)_3I^{-}$
(±)-**3**: X = S→O; R = $N(CH_3)_2$
(±)-**2**: X = SO_2; R = $^{+}N(CH_3)_3I^{-}$
(±)-**4**: X = SO_2; R = $N(CH_3)_2$

First, the molecular structure of (±)-**1** is very close to that of muscarine, a potent and selective muscarinic agent. Moreover, (±)-**1** shows lower affinity but higher efficacy than the parent compound, a fact that has suggested a role for the sulfoxide function in receptor activation.[6] Finally, *cis*-oxathiolane and oxathiolane sulfoxide behave, pharmacologically speaking, much like the muscarone/muscarine couple[7] whose intriguing structure–activity relationships are not yet clearly understood.[8]

Equally interesting, although much less potent as a muscarinic agonist, is the product of further oxidation of (±)-**1**, *cis*-2-methyl-5-[(dimethylamino)methyl]-1,3-oxathiolane 3,3-dioxide methiodide ((±)-**2**, *cis*-oxathiolane sulfone[5]), which is more potent as a nicotinic agent, the muscarinic selectivity present in (±)-**1** being in this case reversed.

We thought it of interest to study the enantioselectivity of the optical isomers of **1** and **2**. To this end it was necessary to obtain the pure enantiomers (+)- and (-)-**1** and (+)- and (-)-**2** and to establish their absolute configurations. This goal was achieved by resolving the racemate of (±)-**3** (the norbase of (±)-**1**) with standard methods, while (+)- and (-)-**2** were obtained by synthesis, which also provided the absolute configurations of the four enantiomers.

Resolution of (±)-3 and Synthesis of (-)- and (+)-1. Resolution was conveniently achieved by treatment of the tertiary amine (±)-**3** with D-(+)- and L-(-)-*O,O'*-di-

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