stant rate of exchange of the alkyl group, is equally applicable to reactions of the form shown in eq 3, 4, and 5, provided the dioximato ligands have equal influence on the rate of exchange.[11] The latter proviso is supported by the observed random ratio of organocobalt(III) complexes, II, III, and V in the equilibrium mixture.

$$RCo(dmgH)_2py + Co(dmgH)(chgH)py \rightleftharpoons RCo(dmgH)(chgH)py + Co(dmgH)_2py \quad (4)$$

$$RCo(chgH)_2py + Co(dmgH)(chgH)py \rightleftharpoons RCo(chgH)(dmgH)py + Co(chgH)_2py \quad (5)$$

(14) The reverse of reaction 3 and the forward and reverse reactions 4 and 5 must similarly be second order.
(15) G. N. Schrauzer and E. Deutsch, *J. Am. Chem. Soc.*, 91, 3341 (1969).
(16) C. K. Ingold, *Quart. Rev., Chem. Soc.*, 11, 1 (1957).
(17) The resonance of H-2 (δ 2.29) is clearly visible (Figure 2) in CH_2Cl_2, whereas that for H-1 (δ 1.84) is partly obscured by the broad upfield resonance of the cyclohexanedionedioximato ligand.
(18) The corresponding coupling constant observed[19] for IIIg was 13.1–13.2 Hz.
(19) P. L. Bock and G. M. Whitesides, *J. Amer. Chem. Soc.*, **96**, 2826 (1974); H. L. Fritz, J. H. Espenson, D. A. Williams, and G. A. Molander, *ibid.*, **96**, 2378 (1974).
(20) The initial erythro organocobalt complex (IIe eq 6), prepared from *threo*-[1-^{2}H-2-^{2}H]-2-phenylethyl 4-toluenesulfonate, contained less than 10% of the corresponding threo diastereoisomer (IId, eq 6). The observation, in the ^{1}H nmr spectrum of the subsequently formed mixture (Figure 2, spectrum a), of coupling constants ascribed to both threo and erythro diastereoisomers is novel and provides a further example, and additional proof, of the inversion of configuration which occurs when an organocobalt(III) complex is formed from an organic ester and a nucleophilic dioximatocobalt(I) reagent (in this case $Co(chgH)_2py^-$).
(21) D. Dodd, B. L. Lockman, and M. D. Johnson, unpublished observations.
(22) A. J. Beckwith and G. Moad, *J. Chem. Soc., Chem. Commun.*, 472 (1974), and references cited therein.

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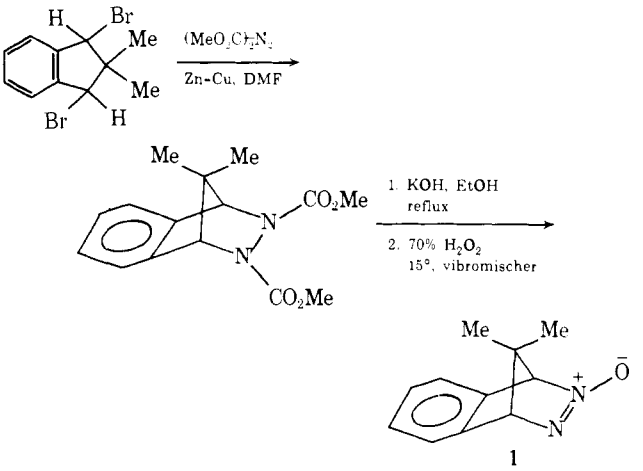
An Intramolecular [1,5]Sigmatropic Alkyl Shift in the Isoindene System

Sir:

Recently, it was demonstrated by Willcott and Rathburn that the thermal [1,5] methyl shift of 1,5,5-trimethylcyclopentadiene was, to a significant extent, an *inter*molecular process.[1] While isomerizations of spirodienes, such as that of the spiro[4,4]nona-1,3-diene system,[2] must undoubtedly proceed intramolecularly, Willcott's results raised the question as to whether any *potentially intermolecular* [1,5] alkyl shift processes are indeed intramolecular. We wish to report at this time the first unambiguous example of such an intramolecular process.

2,2-Dialkyl-substituted 2*H*-indenes seemed to be particularly attractive molecules for use in a systematic study of intramolecular, sigmatropic [1,5] alkyl shifts because: (a) the gain of aromaticity in such rearrangements should induce them to occur with relatively low activation energies, (b) subsequent H-shift processes possibly might be noncompetitive due to the resultant loss of aromaticity, and (c) the nature of the system facilitates identification of the migrating group when two *different* groups are available. The most significant problem in utilizing this system was the devising of a method whereby the isoindene species could be generated under conditions whereby its unimolecular processes might be competitive with its recognized, facile bimolecular processes. This problem was solved by utilizing a smooth, retro[2 + 4] process to generate the isoindene species.

Azoxy species **1** was synthesized from 1,3-dibromo-2,2-dimethylindane[3] by a modification of Snyder's method.[4]



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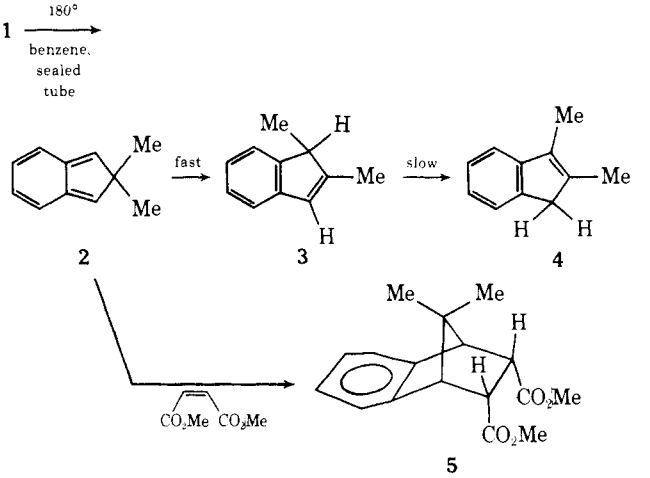
A 0.05 *M* solution of **1** in benzene extruded N_2O at 180°, exhibiting therein a half-life of about 40 min.[5] The transient 2,2-dimethyl-2*H*-indene (**2**) thus generated was found



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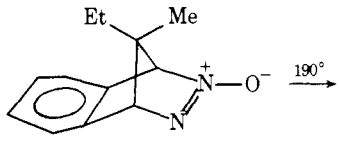
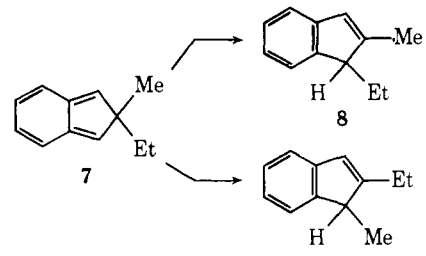
to undergo a smooth [1,5] methyl shift to form 1,2-dimethylindene (**3**). **3** was relatively stable, on this time scale, at 180° to subsequent [1,5] hydrogen shifts,[7,8] but, with adequate time or higher temperatures, the thermodynamically more stable 2,3-dimethylindene (**4**) was formed from **3**. After 3 hr at 180°, the ratio of **3**:**4** was 20:1, while after 1.33 hr at 204° this ratio was 2:1. The glpc determined yield (~80%) of the products was found to be insensitive to (a) temperature of reaction (180–204°), (b) concentration (0.02–0.05 *M*), and (c) time of reaction (0.5–3 hr). The latter observation indicated that N_2O extrusion is rate determining, the rate of the sigmatropic process thus not able to be measured directly. Also there is *no* decrease in yield when cumene was utilized as solvent for the reaction, this speaking strongly against a free-radical-chain mechanism being involved in the rearrangement process.

Concerted transformation of **1** to **3** was ruled out by the observation that intermediate **2** could be trapped efficiently by various dienophiles under the reaction conditions. For example the presence of an equal molar amount of dimethyl maleate diverted 75% of the reaction to adduct **5**.[9] The observed stereospecificity of this Diels–Alder reaction indicates that **3** is behaving similar to a simple diene in this respect, rather than as a triplet species.

The possibility of a chain process being involved was conclusively ruled out by a crossover experiment. Azoxy species **6**, consisting of a mixture of the 7-position epimers,[10] fragmented to the 2-ethyl-2-methyl-2*H*-indene (**7**) which underwent [1,5]sigmatropic alkyl shift to yield exclusively a



6



7 8 9

mixture of indenes **8** and **9**. A quantitative glpc analysis indicated the presence of less than 0.2% of crossover product **3**. Thus one can convincingly rule out the significant intervention of a free-radical-chain process in the rearrangement. Moreover, the ratio of **8**:**9** should be a reflection of the relative migratory aptitude of the ethyl vs. the methyl group in such suprafacial, concerted, thermal sigmatropic rearrangements. A measurement of relative migratory abilities in such processes has hitherto not been reported. Interestingly, the ethyl groups migrated at a rate seven times that of the methyl group. Insight into the factors involved in determining migratory aptitudes in such processes will no doubt be revealed through a systematic study, such as is presently underway.

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References and Notes

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(5) In contrast, the analogous azo compound would be expected to extrude N_2 at temperatures below 0°.[6]
(6) C. R. Flynn and J. Michl, *J. Am. Chem. Soc.*, **96**, 3280 (1974).
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(9) With larger excesses of dienophile, essentially all of the sigmatropic process could be quenched.
(10) Nmr analysis indicates a threefold preference of the isomer shown.

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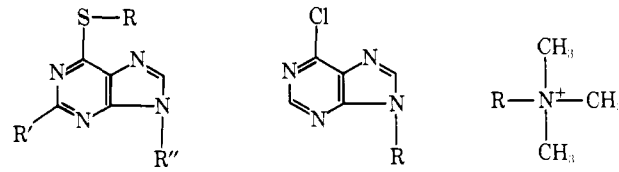
A Comment on Structure–Activity Correlations Obtained Using Pattern Recognition Methods

Sir:

Recently, pattern recognition techniques[1-3] have been applied to the screening of prospective anticancer drugs[4] which had previously been tested for activity in the Adenocarcinoma 755 (CA 755) screening system by the National Cancer Institute.[5] We wish to report that investigation of the structure–activity correlations resulting from this work has led us to conclude that there is a possibility of obtaining misleading relationships when using pattern recognition methods—particularly if there has been no interaction between a chemist and the data.

When we compared the 20 structure–activity correlations obtained for anticancer activity[6] with the structure–activity data of the compounds used to construct these correlations,[7] we observed a number of instances where the addition of one or more "+" correlation features had little effect on the activity and also several examples where the addition of a "+" feature or the replacement of a "+" feature by a different "+" feature caused significant reduction in activity. During this preliminary investigation, it became apparent that structure (1) (where R = H or organic side chain, R′ = H or NH_2, and R″ = H or a furanoside or pyranoside derivative) correlated strongly with anticancer activity. Analysis of the 233 nontoxic compounds in this test[8] revealed the following. (i) There were 80 compounds with structure **1**, 74 of

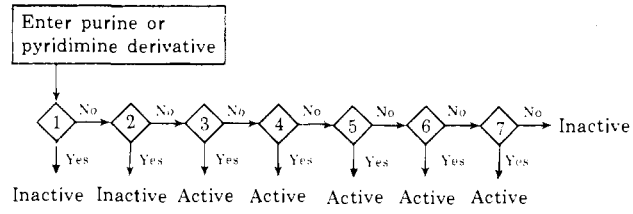


1 2 3

which were active. Five of the six inactive compounds of this structure contained either "fatty acid" or 2,3-*O*-isopropylideneribofuranosyl side chains. Of the 223 compounds, eight contained one or other of these two features and all were inactive. Only in structure **1** was sulfur active; all 13 compounds containing sulfur in other structures were inactive. (ii) Of the remaining 130 compounds which did not contain sulfur, 27 were active. Four of the 130 compounds contained fluorine (three of them active), 14 contained chlorine (seven active), 11 contained bromine (two active), and five contained iodine (all five active). Each of the seven active chlorine compounds and none of the inactive ones had structure 2 (R = ribofuranosyl or pyranosyl derivative). (iii) There were 10 active compounds that did not have structure **1** or contain a halogen. Five of these had structure **3** (R = substituted nucleoside). None of the other 218 compounds being investigated had this structure. (iv) There were no obvious structure–activity correlation features in the remaining five active compounds.

Using correlations based on the above analysis, we have constructed a flowchart (Scheme I) for the classification of the activity of prospective anticancer drugs. This scheme correctly classified 94 of the 101 "positive" (i.e., active) category and 119 of the 122 "negative" (i.e., inactive) cate-

Scheme I. Classification Flowchart



1. Presence of 2,3-*O*-isopropylideneribofuranosyl.
2. Presence of $-(CH_2)_{n-}$, where $n \geq 6$
3. Presence of structure 1, R = H or organic side chain
   R′ = H or NH
   R″ = H, furanoside, or pyranoside derivative
4. Presence of iodine
5. Presence of fluorine
6. Presence of structure 2, R = H, furanoside, or pyranoside derivative
7. Presence of structure 3, R = nucleoside derivative.