derived from primary, purely aliphatic, nitro compounds have half-lives of the order of *ca.* 1 day for the more stable stereoisomer and *ca.* 1 hr. for the less stable stereoisomer. Nitronic esters derived from secondary nitro compounds are apparently less stable than those obtained from primary nitro compounds. Thus, both stereoisomers of the ethyl nitronic ester from 2-nitrobutane (they are produced in equal amounts) in carbon tetrachloride at room temperature have half-lives of only 80 min. Least stable of all is the ethyl nitronic ester derived from nitrocyclohexane which cannot be brought to room temperature without decomposing rapidly.

Extensions of this new synthesis of nitronic esters are being explored and the chemistry of these compounds is under investigation.

Acknowledgments.—We take pleasure in acknowledging the support of the U. S. Army Research Office (Durham). We are indebted to Mr. William E. Baitinger for determining many of the n.m.r. spectra and to Mr. Baitinger and Professor Norbert Muller for much assistance in interpreting these spectra. Satisfactory analyses for the compounds listed in Table I were obtained by Dr. C. S. Yeh, Mrs. T. Eikeri, Mrs. M. Hudgens, Mrs. V. Keblys and Mrs. A. Seo. We deeply appreciate Dr. Yeh's gracious coöperation in making special arrangements for the analyses of these rather unstable compounds.

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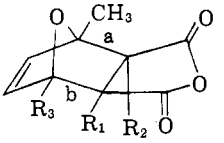
THE MECHANISM OF A DIELS–ALDER REACTION[1]

Sir:

Previously, we reported[2] the isotope effects $k_I/k_{II} = 1.16$ and $k_I/k_{III} = 1.08$ in the decomposition of the Diels–Alder adduct from 2-methylfuran and maleic anhydride. It was impossible, from these results, to differentiate between a stepwise or concerted bond breaking. We now show that bonds a and b break



I, $R_1 = R_2 = R_3 = H$
II, $R_1 = R_2 = D$, $R_3 = H$
III, $R_1 = R_2 = H$, $R_3 = D$
IV, $R_1 = D$, $R_2 = R_3 = H$
V, $R_1 = R_3 = H$, $R_2 = D$

simultaneously.

Preparation of pure IV or V is precluded by the high lability ($t_{1/2} \cong 28$ min. at 50°)[2,3] of this adduct. Fortunately, however, the n.m.r. spectrum of *I* shows protons, R_1 and R_2, to be represented by an AB quartet with $J_{R_1R_3} = 0$ ($J_{R_1R_2} \cong 7.2$ c.p.s., $\tau_{R_1} = 6.71$, $\tau_{R_2} = 6.96$, in $CHCl_3$).[4] The quartet disappears in II, is unaltered in III, and becomes a doublet in a mixture of IV and V. The ratio of the peak areas in the doublet is then equal to the molar ratio of IV to V. Determinations of this ratio initially and after a large extent of decomposition yield[5] the isotope effect, k_{IV}/k_V, which determines[6] the relative amount of bond breaking of a compared to b in the slow step.

Monodeuteriomaleic acid was prepared by electrolytic dehalogenation of sodium bromomaleate in D_2O (lead cathode, ~15°) and converted to the anhydride as reported.[7] Preparation of the IV–V mixture is similar to that for I.[2]

The IV–V mixture (m.p. 75–76°) in 30% dioxane–70% isoöctane decomposed at 50° for a specified time, then was cooled in ice and the solvent (and 2-methylfuran) was removed rapidly at reduced pressure. Maleic anhydride sublimed (oil pump) and the adduct residue was either recrystallized or sublimed under high vacuum. N.m.r. determinations of IV/V before and after a large extent of reaction are recorded in columns 2 and 4 of Table I.

TABLE I
N.M.R. DETERMINATION OF ISOTOPE EFFECT

$[IV + V]_0$	$[IV]_f/[V]_f$[a] obsd.	% Reaction	$[IV]_f/[V]_f$[a] obsd.	$[IV/V]_f/[IV/V]_0$ calcd. One step	$[IV/V]_f/[IV/V]_0$ calcd. Two steps[b]
0.1132 *M*	1.00 ± 0.02	87	0.99 ± 0.04	1.00	1.31
.0959 *M*	1.02 ± .06	81	1.00 ± .04	1.00	1.24
.0796 *M*	1.01 ± .02	82	1.00 ± .04[c]	1.00	1.25

[a] Each ratio is the average of 20 or more integrations. Errors are average deviations. [b] Calculated by an equation given by Bigeleisen and Wolfsberg.[5] [c] Adduct purified by high vacuum sublimation.

If the effect, $k_I/k_{II} = 1.16$, is mainly due to deuteriation at R_1 (*i.e.* bond b breaks in a slow step and a in a prior or latter rapid step) then after large conversion the remaining substrate would be richer in IV than in V. The ratios of final to initial (IV/V) are given in column 6 of Table I for a hypothetical $k_V/k_{IV} = 1.15$ (*i.e.*, a two-step reaction). For equal amount of bond-breaking of a and b at the transition state (*i.e.*, one-step concerted reaction), this ratio becomes 1.00 (column 5) because the effect, k_V/k_{IV}, would equal 1.00. The results shown indicate that reversion conforms closely to a concerted rupture of a and b.

TABLE II
DETERMINATION OF DEGREE OF REVERSIBILITY DURING DECOMPOSITION OF 4-METHYL-7-OXA-BICYCLO[2.2.1]-2-HEPTENE-EXO-5,6-DICARBOXYLIC ACID ANHYDRIDE

Adduct[a] *M*	Maleic anhydride-2,3-C^{14}[b] $M \times 10^3$	% Reaction	Calcd. %[f] reformed adduct	Sp. activity in remaining adduct mμC/mgC	Observed %[g] reformed adduct
0.0940[c]	5.78	77.7	8.2	0.490	17.9
.0194[d]	1.25	78.8	1.5	.421	14.6
.0743[e]	3.52	78.6	6.9	.411	19.0

[a] Adduct obtained by sublimation of the solid residue after evaporation of solvent, except see *e*. [b] Initial specific activity = 85.7 mμC/mgC. [c] V_0 = 250 ml. (30% dioxane in isoöctane). [d] V_0 = 1200 ml. (27% dioxane in isoöctane). [e] Reaction mixture immediately cooled; solvent lyophillized and adduct sublimed from the solid residue. V_0 = 304 ml. (100% dioxane). [f] Calculated from the amount of reverse reaction as

$$A \xrightarrow{k_1} B + C \quad (1) \qquad A \underset{k_1}{\rightleftharpoons} B + C \quad (2)$$

From (1), $A_t = a_0 e^{-k_1 t}$

From (2), $\ln \frac{2k_2x + k_1 + k_2b_0 + S}{2k_2x + k_1 + k_2b_0 - S} \times \frac{k_1 + k_2b_0 - S}{k_1 + k_2b_0 + S} = St$

where $S = \sqrt{(k_1 + k_2b_0)^2 + 4k_1k_2a_0}$, $A_2 = a_0 - x$ and the other notations have their usual meanings. Then calcd. % reformed adduct = $(A_2 - A_1)/A_1 \times 100$. [g] (Sp. activity in adduct × 9/4 × 100)/(sp. activity in diluted maleic anhydride at −% reaction).

The ratio, $[IV/V]_f$, should refer to unreacted substrate and not to adduct reformed during decomposition. Reversibility was checked for in two ways: (1) by looking for C^{14}-incorporation in the adduct after partial

(1) Work performed under the auspices of the U. S. Atomic Energy Commission.

(2) S. Seltzer, *Tetrahedron Letters*, **No. 11**, 457 (1962).

(3) See, *e.g.*, R. B. Woodward and H. Baer, *J. Am. Chem. Soc.*, **70**, 1161 (1948).

(4) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961); M. M. Anderson and P. M. Henry, *Chem. Ind.* (London), 2053 (1961).

(5) J. Bigeleisen and M. Wolfsberg, in "Advances in Chemical Physics," Vol. I, I. Prigogine, Ed., Interscience Publishers, Inc., New York, N. Y., 1958, p. 38.

(6) A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey and S. Suzuki, *J. Am. Chem. Soc.*, **80**, 2326 (1958); S. Seltzer, *ibid.*, **83**, 2625 (1961); **85**, 14 (1963).

(7) S. Seltzer, *ibid.*, **83**, 1861 (1961).

reversion in the presence of maleic anhydride-2,3-C^{14}; and (2) by determining an approximate equilibrium constant [K = 1.7 M = (maleic anhydride)(2-methylfuran)/(adduct)] from the integrated n.m.r. spectra of reactants and product in CCl_4. Column 4 of Table II gives the % remaining adduct resulting from readdition as calculated from the equilibrium constant. Column 6, alternatively, gives the % reformed adduct as determined by C^{14}-incorporation. Here, one assumes that return only occurs during work up (*i.e.*, concentration after decomposition has been quenched). The specific activity of added maleic anhydride-C^{14} decreases as adduct-decomposition progresses. Therefore return of a maleic anhydride-C^{14}-molecule after 80% reaction is accompanied with more return of natural anhydride than one returning after 30% reaction. Hence the figures in column 6, Table II, represent the *maximum* possible return; the true degree of reversibility is somewhere between the values given in columns 4 and 6. Since there was no initial maleic anhydride present, the amount of return, in the runs of Table I, is less than the figures of Table II.

For a two-step adduct-decomposition, k_V/k_{IV} was assumed to be 1.15. One might expect the reciprocal, 0.87, for the isotope effect of the reverse reaction. The ratio, [IV]/[V], from return should be independent of extent of return and equal to 1.15. If 15% of the isolated adduct comes *via* return then the observed effect would have led to $0.15[(IV/V)_{returned} = 1.15] + 0.85[(IV/V)_{unreacted} \cong 1.3] = 1.28$. Therefore, the small amount of adduct that comes from readdition during decomposition of the adduct does not affect the conclusion that both a and b are breaking simultaneously in the slow step. From the principle of microscopic reversibility, the formation of this Diels–Alder adduct involves forming bonds a and b simultaneously.[8]

Acknowledgment.—We acknowledge, with appreciation, the discussions with and help given by Dr. Gerald Dudek, Harvard University, in the n.m.r. studies.

(8) For a discussion of this problem see: A. Wasserman, *J. Chem. Soc.*, 612 (1942); C. Walling and J. Peisach, *J. Am. Chem. Soc.*, **80**, 5819 (1958); R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959); J. A. Berson, A. Remanick and W. A. Mueller, *J. Am. Chem.Soc.*, **82**, 5501 (1960); J. A. Berson and W. A. Mueller, *ibid.*, **83**, 4940 (1961), **83**, 4947 (1961); M. S. Newman, *J. Org. Chem.*, **26**, 2630 (1961); M. G. Ettlinger and E. S. Lewis, *Texas J. Sci.*, **14**, 58 (1962); J. Sauer, D. Lang and A. Mielert, *Angew. Chem. Intern. Ed. Engl.*, **1**, 268 (1962); R. P. Lutz and J. D. Roberts, *J. Am. Chem. Soc.*, **83**, 2198 (1961).

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RECEIVED JANUARY 17, 1963

THE STRUCTURE, CONFIGURATION AND SYNTHESIS OF THALICARPINE, A NOVEL DIMERIC APORPHINE-BENZYLISOQUINOLINE ALKALOID[1]

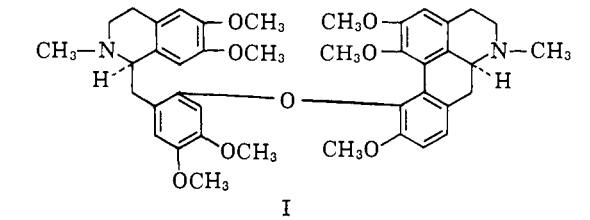
Sir:

Thalicarpine is a hypotensive alkaloid from *Thalictrum dasycarpum* Fisch. and Lall, and its isolation and preliminary characterization have recently been reported.[2] The elucidation of structure and absolute configuration I and the total synthesis of thalicarpine are reported herewith. Thalicarpine represents a novel type of alkaloid; it appears to be the first recognized dimeric alkaloid which contains an aporphine moiety.

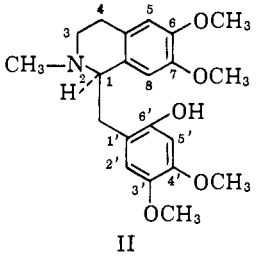
Thalicarpine (I), $C_{41}H_{48}O_8N_2$, m.p. 160–161°, $[\alpha]^{25}D$ +89°,[3] shows λ_{max} 282 mμ (ε 17,000), 302 mμ (ε 13,000) and n.m.r. peaks[4] 7.55, 7.52 (6H, two NCH_3), 6.40, 6.29, 6.21, 6.19, 6.17, 6.09, 6.05 (21H, seven OCH_3), 3.79, 3.47, 3.40, 3.37, 3.32, 1.77 τ (7H, aromatic). Hofmann degradation[2] yielded a methine which was characterized as the dimethiodide, $C_{45}H_{58}O_8N_2I_2 \cdot H_2O$, m.p. 275–276°. A second Hofmann degradation yielded the *des*-N-methine,[2] $C_{39}H_{38}O_8$, m.p. 170–172°.

Sodium in liquid ammonia reduction of I afforded (−)-6′-hydroxylaudanosine (II) and (+)-3,6-dimethoxyaporphine (III), both in amorphous form. II was characterized as the hydriodide, $C_{21}H_{27}O_5N \cdot HI \cdot H_2O$, m.p. 184–186°, $[\alpha]^{26}D$ −71° (methanol), and the O-methylmethiodide, $C_{23}H_{32}O_5NI$, m.p. 223–224°, $[\alpha]^{23}D$ +109°. Hofmann degradation of the methiodide gave a methyl methine (IVa), $C_{23}H_{31}O_5N$, m.p. 125–127°, $[\alpha]^{28}D$ ±0°, 282 mμ (ε 19,000), 343 mμ (ε 30,500), mass spectral peaks at *m/e* 401, *m/e* 58.[5] To locate the phenolic hydroxyl group, II was converted to the O-ethylethiodide, which upon Hofmann degradation yielded IVb, $C_{25}H_{35}O_5N$, m.p. 88–89°, $[\alpha]^{27}D$ ±0°; λ_{max} 290 mμ (ε 12,000), 336 mμ (ε 12,600). The methiodide of IVb ($C_{26}H_{38}O_5NI$, m.p. 201–202°) was treated with methanolic alkali to yield the *des*-N-methine, $C_{22}H_{26}O_5$, m.p. 129–130°. Oxidation of the *des*-N-methine with potassium permanganate gave 2-ethoxy-4,5-dimethoxybenzoic acid.[6]

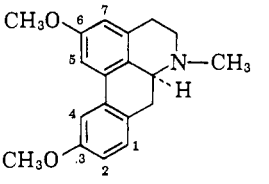
III was characterized as the methiodide,[7] $C_{20}H_{24}O_2NI$, m.p. 164–166°, $[\alpha]^{25}D$ +66° (methanol), and the Hof-



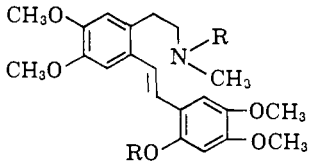
I



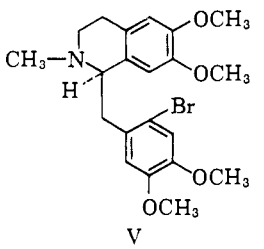
II



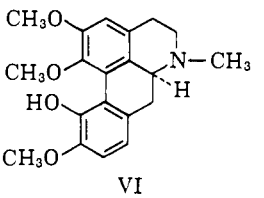
III



IVa, R = CH_3
b, R = CH_3CH_2



V



VI

(1) This is part II of a series entitled "Thalictrum Alkaloids"; part I is ref. 2.

(2) S. M. Kupchan, K. K. Chakravarti and N. Yokoyama, *J. Pharm. Sci.*, in press.

(3) Rotations and infrared spectra are in chloroform unless otherwise noted. All ultraviolet spectra are in methanol.

(4) N.m.r. spectra were determined on a Varian Associates recording spectrometer (A-60) at 60 Mc. in deuterated chloroform. Chemical shifts are reported in τ values (p.p.m.) [G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958)].

(5) We thank Professor K. Biemann and Dr. B. C. Das, Massachusetts Institute of Technology, for the mass spectral data.

(6) J. B. D. Mackenzie and A. Robertson, *J. Chem. Soc.*, 497 (1949). We thank Professor W. B. Whalley, School of Pharmacy, University of London, for an authentic sample of 2-ethoxy-4,5-dimethoxybenzoic acid.

(7) T. Kitamura, *J. Pharm. Soc. Japan*, **80**, 1104 (1960).