1-Methylazepine-2,7-dione. Synthesis and Reactions

ROBERT SHAPIRO AND STEPHEN NESNOW[1]

Department of Chemistry, New York University, New York, New York 10003

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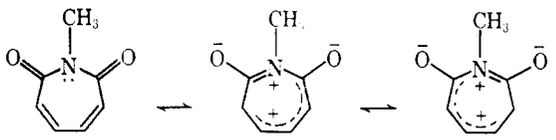
1-Methylazepine-2,7-dione (1), the first simple derivative of the azepine-2,7-dione system, has been synthesized. This was accomplished by dehydrohalogenation of *trans*-3,6-dibromo-1-methyladipimide (**4**), prepared by the reaction of cupric bromide with 1-methyladipimide (**3**). Three reactions of **1** were investigated. Bromination yielded 5,6-dihydro-5,6-dibromo-1-methylazepine-2,7-dione. The Diels–Alder reaction of **1** with cyclopentadiene gave both an *exo* and *endo* adduct. Ethanolysis of **1** yielded ethyl N-methyl-*cis*,*cis*-muconamate (**7**). The saturated analog of **1**, compound **3**, did not react under identical conditions. Hydrogenation of **7** gave ethyl N-methyladipamate which was also synthesized by a different route. The properties of **1** are compared to several aromatic analogs and the results are discussed.

We have been interested in the properties of unsaturated heterocyclic systems, particularly with respect to their chemical reactivity and aromaticity. The azepinedione system is of interest because of its resemblance to the resonance-stabilized systems, 2-pyridone and tropone. The preparation of derivatives of 1H-azepine-2,5-dione has been reported,[2-4] but only the dibenzo derivative of azepine-2,7-dione is known.[5,6] We desired to prepare 1-methylazepine-2,7-dione (**1**) (N-methyl-*cis*,*cis*-muconimide) because, as a simple derivative of the parent system, it would afford unambiguous measurement of the properties we sought to investigate. If this 6π-electron system is stabilized by resonance of the aromatic type, the resonance hybrid would contain appreciable contributions of the canonical structures indicated. These structures are similar to those postulated for tropone.



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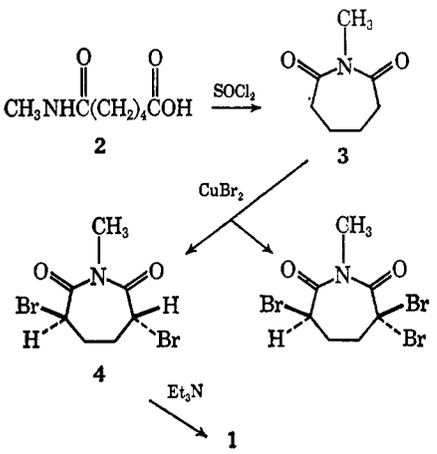
Results and Discussion

Our synthetic scheme first involved the synthesis of the saturated analog, 1-methyladipimide (**3**). Although Flitsch had reported the synthesis of this compound in 30–40% yields by the pyrolysis of N-methyladipamic acid (**2**),[7] our yields upon repetition of his work were much lower and not acceptable. We succeeded in the synthesis of **3** by treating **2** with thionyl chloride and cyclization of the thionyl chloride–acid amide complex to the imide by vacuum pyrolysis (Scheme I). The properties of this compound were identical with those reported by Flitsch.[7] Imide **3** was brominated with cupric bromide[8] to yield two products which were separated by column chromatography on silica and identified as *trans*-3,6-dibromo-1-methyladipimide (**4**) and 3,3,6-tribromo-1-methyladipimide (**5**) from their elemental analyses, nmr and ir spectra. The chemical shifts and relative intensities of **5** in the nmr spectrum unambiguously placed all the three bromines α to the imide carbonyls.[9] The ir spectrum of **5** showed two intense carbonyl bands which were each shifted *ca.* +28 cm^{-1} relative to **3**. In 2-bromocyclohexanone, an equatorial bromine exerts a marked effect on the carbonyl stretching absorbance, +15–22 cm^{-1}, because of the inhibition of resonance stabilization. An axial bromine exerts a minor effect, −3 to +3 cm^{-1}.[10] In all of the possible conformers of **5**, there is always a bromine in a quasi-equatorial (parallel to carbonyl) postion.[11] This accounts for the observed shift. In the nmr spectrum of dibromoimide **4**, the bromines were assigned to C_3 and C_6 upon inspection of the two-proton multiplet at τ 4.90, (C_3, C_6), and the four-proton multiplet at 7.08–8.00. (C_4, C_5). The splitting patterns for both absorbances were very complex, having a total of 48 observed transitions. This complexity was due in part to virtual coupling[12] and conformational effects. The melting point and chromatographic behavior[13] of **4** appeared to indicate that we were dealing

SCHEME I



(1) New York University Special Predoctoral Fellow 1966–1967.

(2) (a) D. Misiti, H. W. Moore, and K. Folkers, *Tetrahedron Lett.*, 1071 (1965); (b) D. Misiti, H. W. Moore, and K. Folkers, *Tetrahedron*, **22**, 1201 (1966).

(3) R. W. Rickards and R. M. Smith, *Tetrahedron Lett.*, 2361 (1966).

(4) G. R. Bedford and G. Jones, *ibid.*, 2367 (1966).

(5) H. W. Underwood, Jr., and E. L. Kochman, *J. Amer. Chem. Soc.*, **46**, 2069 (1924).

(6) The preparation of a trihydroxyiminoazepine derivative has been reported briefly: A. H. Rees, *Chem. Ind.* (London), 1298 (1965). This compound could exist as several tautomers, including azepine-2,4-dione and an azepine-2,7-dione. No full characterization or study of the tautomerism of this compound has as yet appeared.

(7) W. Flitsch, *Chem. Ber.*, **97**, 1542 (1964).

(8) L. C. King and G. K. Ostrum, *J. Org. Chem.*, **29**, 3459 (1964).

(9) The lone hydrogen α to the imide was represented by a quartet, indicating that a potential AMNXY system had simplified to an AMN system. For a discussion of this type of simplification, see ref 18, p 94.

(10) E. G. Cummins and J. E. Page, *J. Chem. Soc.*, 3847 (1957).

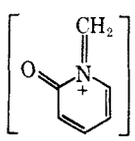
(11) The terms quasi-axial and quasi-equatorial are used in this paper to describe the stereochemical positions found in a seven-membered ring. These, of course, are approximations of the true axial and equatorial positions as found in cyclohexane.

(12) J. I. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1962).

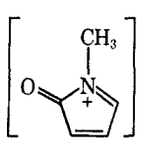
(13) Compound **4** was found to be chromatographically pure on silica in the following systems: chloroform, benzene, chloroform–hexane 80:20, hexane–ethyl acetate 80:20, 50:50.

with a single isomer, *cis* or *trans*. Attempts to assign the stereochemistry of **4** by hydrolysis of it to a known α,α'-dibromoadipic acid were unsuccessful. The ir spectrum did provide useful information, however. The carbonyl stretching absorbances in **4** are shifted *ca.* +7 cm^{-1} relative to **3**. In light of the previous discussion, this would indicate that the predominant conformer of **4** has no quasi-equatorial bromines. Examination of models reveal that *trans* **4** has such a conformer, while *cis* **4** has not. The *trans* structure was therefore assigned to **4**.

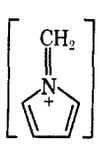
1-Methylazepine-2,7-dione (**1**) was formed by dehydrohalogenation of **4** with triethylamine. The product was separated by preparative thin layer chromatography on silica gel. The mass spectrum of **1** was consistent with its structure. Fragments of *m/e* 109 and 81 corresponded to the loss of one and two C=O units, and are postulated to represent radical ions derived from N-methyl-2-pyridone and N-methylpyrrole. Loss of C=O from systems of this type is well known.[14a,b] Although the exact electronic structure of the daughter ion formed in the M—C=O decomposition is still in question,[14c,d] it is likely that the suggested structures do comprise some portion of this ion. Postulated structures for other major fragments (*m/e* >60, relative abundance >15%, 70 eV) are shown (**6a, b, c**). The loss of hydrogen radical from



6a, *m/e* 108



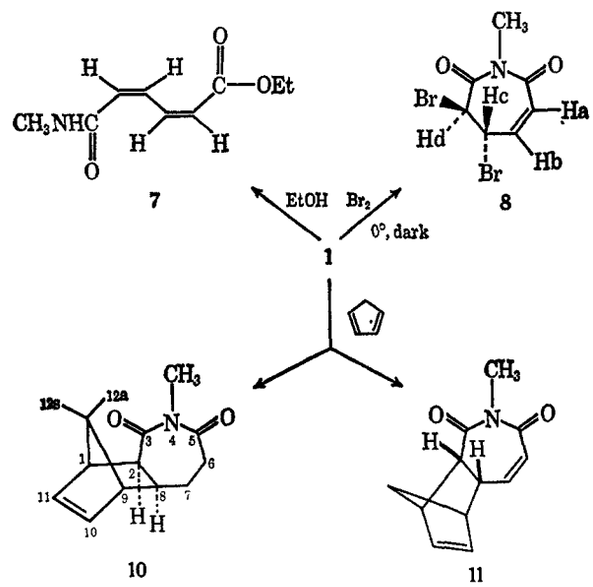
6b, *m/e* 96



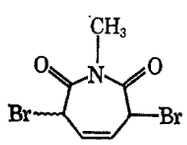
6c, *m/e* 80

1-methyl-2-pyridones to give fragments corresponding to **6a** has been reported.[14e] It is interesting to note that the mass spectrum of **1** contains every major peak found in the spectrum of 1-methyl-2-pyridone.[14e] The nmr spectrum of **1** shows a striking case of solvent effect. In deuteriochloroform, **1** exhibited two singlets (τ 3.37, 4 H; 6.64, 3 H). In deuteriobenzene, however, the low-field singlet is expanded into an AA'BB' spin pattern, similar in shape to that observed for phenazine.[15] The coupling contants and chemical shifts were calculated[16] by computer using a modified version of the LAOCN3 program[17] and were found to be $J_{aa'} = 7.72 \pm 0.16$; $J_{bb'} = 0.58 \pm 0.14$; $J_{ab} = 12.33 \pm 0.16$; $J_{ab'} = 1.56 \pm 0.15$; $\nu_a = 382.1 \pm 0.10$; $\nu_b = 346.4 \pm 0.10$ Hz. The infrared spectrum of **1** suggested a conjugated imide: the two carbonyls were shifted to lower wave number (*ca.* 60 cm^{-1}) relative to **3**. The ultraviolet spectrum showed a strong band at 220 mμ (ϵ 15,200) and a moderate one at 287 mμ (ϵ 3620) indicative of a conjugated system. The azepine-2,5-dione system shows two absorbances quite similar to these but in addition another maximum above 300 mμ.[3] The first reaction of **1** to be investigated was bromination (Scheme II). Although bromination of **1** in chloro-

SCHEME II



form at ambient temperature gave a mixture of products, bromination conducted in ice-cold hexane in the dark yielded only one product identified as *trans*-5,6-dihydro-5,6-dibromo-1-methylazepine-2,7-dione (**8**). The assignment of structure was based on interpretation of its ir and nmr spectra. There are two normal modes of addition that can occur in this system—1, 2 and 1,4 addition. These would yield products **8** and **9**,



9

respectively. The ir carbonyl stretching absorptions fit structure **8** better than **9**; **9** should have relatively the same values as **4** because they are similar in structure. The carbonyl frequencies observed were much lower, indicating that the unsaturation was conjugated with the carbonyl group. The nmr spectrum taken in deuteriobenzene was definitely a first-order spectrum. It obeyed the condition for first-order approximations, *i.e.*, $\Delta\nu > 6J$.[18,19] Multiplets were observed for four distinctly different kinds of protons. This eliminated the possibility of 1,4 addition, **9**, because it should have exhibited an AA'XX' or possibly an AA'BB' pattern, both of which have specific symmetry elements not found in this spectrum. We assign in **8**: τ 4.00 to H_a;

(14) (a) H. Budzikiewicz, C. Djerassi, and D. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, pp 359, 571; (b) C. Nolde, S.-O. Lawesson, J. H. Bowie, and R. G. Cooks, *Tetrahedron*, **24**, 1051 (1968); (c) W. T. Pike and F. W. McLafferty, *J. Amer. Chem. Soc.*, **89**, 5954 (1967); (d) M. M. Bursey and L. Dusold, *Chem. Commun.*, 712 (1967); (e) R. Lawrence and E. S. Waight, *J. Chem. Soc., B*, 1 (1968).

(15) T. K. Lim, A. Taurins, and M. A. Whitehead, *Can. J. Chem.*, **44**, 1211 (1966).

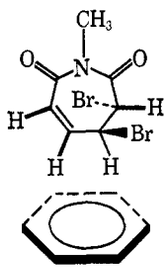
(16) The root mean square error in line fitting was 0.414.

(17) LAOCN3 is the recently revised version of the LAOCOON II program described in S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, **41**, 3863 (1964).

(18) R. Bible, "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, p 48.

(19) The only value below this ratio is $\Delta\nu_{ab}/J_{ab} = 2.75$. This intermediate value seems to affect only the relative line intensities of both patterns, decreasing the outer lines and increasing the inner ones; *cf.* the spectrum of 4-vinylpyridine: N. S. Bhacca, L. F. Johnson, J. N. Schoolery, "High Resolution NMR Spectra Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., 1962, No. 155.

4.55 to H_b; 5.32 to H_d; 6.35 to H_c; and J_{ab} = 12.1 Hz; J_{bc} = 7.0 Hz; J_{bd} = 1.4 Hz; J_{cd} = 5.0 Hz. This assignment of chemical shifts was supported by the observed selective solvent shifts of **8** in deuteriobenzene, as compared to carbon tetrachloride.[20-23] H_b and H_c were shifted 63 cps upfield, and H_a and H_d 20–21 cps upfield. These results can be pictured in terms of the given solvent–solute collision complex. This is consistent with the observation that the benzene molecule aligns itself away from the negative and close to the positive end of the solute dipole.[20-23] A model similar to the above can be found in phthalic anhydride where the α protons are shifted +49 Hz and the β protons +68 Hz.[20]



The magnitudes of J_{ab} and J_{cd} are reasonable for the structures involves.[24] It is unlikely that H_c and H_d are in quasi-diaxial positions, as a larger J_{cd} value might be expected. The value of J_{bc} also suggests that H_c is quasi-equatorial. 3,4-Dibromobicyclo[3.2.1]octa-2-ene, a molecule of fixed geometry, has an allylic coupling constant of 6.6. Hz.[25] The dihedral angle of the protons involved is close to that for H_b and H_c in models of **8** in which H_c is quasi-equatorial. The H_b to H_d coupling observed is an example of the W effect.[26]

In Diels–Alder reactions **1** did not act as a diene, *i.e.*, it did not react with maleic anhydride or tetracyanoethylene. It did act as a dieneophile by reacting with cyclopentadiene at room temperature to form two products which were separated by preparative thin layer chromatography. Both products had identical molecular formulas and very similar ir and uv spectra. The nmr taken in deuteriochloroform showed absorbances at chemical shifts consistent with the formulas, *exo*-4-methyl-4-azatricyclo[7.2.1.$0^{2,8}$]dodeca-6,10-diene-3,5-dione (**10**) and *endo*-4-azatricyclo[7.2.1.$0^{2,8}$]dodeca-6,10-diene-3,5-dione (**11**). The splitting patterns were very complex, probably due to the fact that protons H_6, H_7, H_8, H_2 are strongly coupled with each other. This additional multiplicity hinders assignment of the *exo* or *endo* isomers on coupling constant grounds,[27-29] however, this assignment can be made upon interpretation of the chemical shifts of the bridge protons (H_{12a}, H_{12s}). Models of the isomers show that in the *exo* case the bridge protons could absorb at chemical shifts different from the corresponding protons in *exo*- or *endo*-5-substituted 2-norbornenes (τ 8.44–8.78).[27] The direction of this shift cannot be unequivocally predicted. The chemical shifts of the same protons in the *endo* isomer should be quite close to those of the norbornenes. Indeed in the two nmr spectra, the bridge protons appear in considerably different regions. One isomer exhibited absorbances of τ 7.30 and 7.95 and was assigned the *exo* configuration. The other isomer exhibited an absorbance at τ 8.50 and was assigned the *endo* configuration. Since it is known that in this reversible reaction the *endo* isomer is the kinetic product while the *exo* isomer is the thermodynamic product, we measured the product ratio at a lower temperature. When the reaction was conducted at 0°, the ratio of *exo*/*endo* was 1.37. When compared with a value of 11.70 obtained at 30°, we see that a higher temperature favors the *exo* product. In addition, the *endo* product isomerized to the *exo* one after standing 6 weeks at ambient temperature protected from light. These facts add further support to our assignment. Additional evidence which reinforced this assignment was found in the mass spectra. The mass spectra of the two isomers showed nearly identical *m/e* positions, but very different relative abundances. It would seem that the relative stabilities of the parent and daughter ions in a fragmentation play an important part in determining the probability of such fragmentation. This probability would manifest itself in the rate constant of this fragmentation.[30,31] In our case the *endo* isomer, being more highly strained, would undergo a fragmentation to a less strained ion faster than the *exo* isomer. A good vehicle for this analysis is the $M\cdot^+ - C_5H_5\cdot$ fragmentation. We are assuming that this retro-Diels–Alder reaction is purely an electron impact phenomenon and not thermally initiated.[32] Following Bursey and McLafferty's[33] kinetic approach to mass spectra, we have derived a similar expression which allows us to calculate the ratio of the two fragmentations: $M\cdot^+_{endo} - C_5H_5\cdot$, $M\cdot^+_{exo} - C_5H_5\cdot$. By

$$M\cdot^+_{endo} \xrightarrow[k_{endo}]{-C_5H_5\cdot} A_{endo}^+$$

$$M\cdot^+_{exo} \xrightarrow[k_{exo}]{-C_5H_5\cdot} A_{exo}^+$$

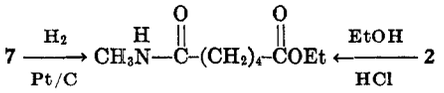
$$\frac{A^+_{endo}/M\cdot^+_{endo}}{A^+_{exo}/M\cdot^+_{exo}} = \frac{k_{endo}}{k_{exo}}$$

substituting the appropriate values we arrive at k_{endo}/k_{exo} = 1.50. This value again supports our assignment of isomers.

Azepinedione **1** reacted with ethanol at ambient temperature in the dark. No catalyst was needed, although catalytic amounts of sodium hydroxide increased the rate of reaction. The product of this reaction was ethyl N-methyl-*cis*,*cis*-muconate (**7**). Conclusive proof of this structure was obtained upon

(20) T. Ledaal, *Tetrahedron Lett.*, 1683 (1968).
(21) R. M. Moriarty and J. M. Kleigman, *J. Org. Chem.*, **31**, 3007 (1966).
(22) K. M. Baker and B. R. Davis, *J. Chem. Soc., B*, 251 (1968).
(23) J. Ronayne and D. H. Williams, *ibid.*, **540** (1967).
(24) R. Silverstein and G. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1967, p 144.
(25) C. W. Jefford, *Proc. Chem. Soc.*, (London), 64 (1963).
(26) (a) J. Feeney, *Ann. Rept. Progr. Chem.*, **63**, 247 (1966); (b) M. Barfield, *J. Chem. Phys.*, **41**, 3825 (1964); (c) S. Sternhell, *Rev. Pure App. Chem.*, **14**, 15 (1964).
(27) J. C. Davis Jr. and T. V. Van Auken, *J. Amer. Chem. Soc.*, **87**, 3900 (1965).
(28) P. Laszlo and P. von R. Schleyer, *ibid.*, **86**, 1171 (1965).
(29) E. I. Snyder and B. Franzus, *J. Amer. Chem. Soc.*, **86**, 1166 (1964).
(30) D. C. DeJongh and S. R. Shrader, *ibid.*, **88**, 3881 (1966).
(31) P. Natalis, *Bull. Soc. Chim. Belges*, **75**, 668 (1966).
(32) H. Budzikiewicz, J. I. Brauman, and C. Djerassi, *Tetrahedron*, **21**, 1855 (1965).
(33) M. M. Bursey and F. W. McLafferty, *J. Amer. Chem. Soc.*, **88**, 529 (1966).

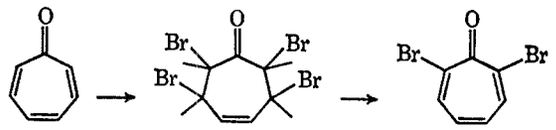
catalytic hydrogenation of **7** on Pt/C which yielded ethyl N-methyladipamate (**12**). Compound **12** was prepared by the reaction of **2** with dry hydrogen chloride in ethanol. The product from the hydrogenation and from the esterification were identical. A point to note



12

is that the ethanolysis and subsequent hydrogenation confirmed that the synthesis of **1** had proceeded without rearrangement. As the conditions of the ethanolysis reaction and work-up were not sufficient to cause isomerization in related systems,[34a] it was assumed that **7** had retained the *cis–cis* stereochemistry of **1**. Examination of the nmr, uv, and ir spectra of **7**, and a comparison of these to similar systems, did not refute or support this assignment.[34,35] The kinetics of the ethanolysis were found to be pseudo first order, $k_{47°} = 9.97 \pm 0.45 \times 10^{-5}$ min^{-1}, by ultraviolet spectroscopy. No reaction was observed when the saturated analog, **3**, was subjected to identical reaction conditions, although the hydrolysis of **3** in alkali has been reported.[36]

It is of interest to consider the physical and chemical properties of **1** with reference to the possible aromaticity of the system. One of the methods of evaluating the extent of aromaticity of a new compound is to compare it with known compounds considered to have aromatic character. Some of the criteria of aromaticity are manifested in the uv and nmr spectra and in the chemical reactivity. Two compounds which are similar to **1** and possess aromatic properties are tropone[37–39] and 1-methyl-2-pyridone.[38–40a] The uv spectra of the compounds, a measure of π electron conjugation, are similar: tropone,[37a] $\lambda_{max}^{H_2O}$ 228 mμ (log ϵ = 4.34), 312.5 (3.92); 1-methyl-2-pyridone,[41] λ_{max}^{MeOH} 227 mμ (log ϵ = 3.64), 300 (3.64); 1-methylazepine-2,7-dione, λ_{max}^{MeOH} 220 mμ (log ϵ = 4.18), 287 (3.56). The nmr spectra, a measure of diamagnetic anisotropy, has also been used in estimating aromatic character.[40] A chemical shift of a ring proton downfield from the expected position has been considered to indicate the existance of an appreciable diamagnetic ring current. The following chemical shifts are for $CDCl_3$ solution. Tropone exhibits an absorption at τ 2.92.[37a] The C_4 and C_6 ring



protons of 1-methyl-2-pyridone absorb at τ 2.74 and 2.69, respectively.[40a] 1-Methylazepine-2,7-dione shows absorption at τ 3.37. This greater shielding suggests the existance of a lesser diamagnetic ring current in **1** than in tropone or 1-methyl-2-pyridone. A comparison of chemical properties shows that tropone undergoes addition of bromine to yield 2,3,6,7-tetrabromo-4-cycloheptenone, which loses hydrogen bromide upon heating to give 2,7-dibromotropone.[42] 1-Methyl-2-pyridone reacts with bromine to give the substituted product, 3,5-dibromo-1-methyl-2-pyridone.[43] Although an addition–elimination sequence cannot be excluded for this reaction, no intermediate was reported. Tropone reacts both as diene (with maleic anhydride) and as dienophile (with 1,3-cyclohexadiene)[42] while 1-methyl-2-pyridone was found not to react with maleic anhydride.[40a] Although 1-methyl-2-pyridone does not undergo ring opening with alkali[40a] 2-halotropones undergo a facile ring contraction to benzoic acid derivatives in an alkali-catalyzed reaction.[37] We conclude that both the chemical and physical properties show that 1-methyl-2-pyridone seems to be more aromatic than tropone which in turn is slightly more aromatic than 1-methylazepine-2,7-dione (**1**).

Experimental Section

Melting points were determined on a Thomas–Hoover apparatus and are uncorrected. Ultraviolet spectra were determined with a Perkin-Elmer Model 202 spectrophotometer or Beckman DU, infrared spectra with a Perkin-Elmer Model 137 or Baird-Atomic Model 1455, nmr with a Varian A-60 using tetramethylsilane as internal reference (τ 10). Analyses were performed by Mr. George Robertson Jr., Florham Park, N.J., Spang Microanalytical Laboratory, Ann Arbor, Mich., or by an F & M Elemental Analyzer, Model 185. Mass spectra were determined with a Varian M-66 employing a direct inlet system. Thin layer chromatography was performed on plates prepared with Adsorbosil-1 (Applied Science Laboratories, State College, Pa.) to which approximately 5% Radelin phosphor GS-115 had been incorporated. Plates were visualized with an ultraviolet lamp equipped with a short wave filter. Gas chromatography was performed on a Varian-Aerograph Model 90P-3.

1-Methyladipimide (3).—N-Methyladipamic acid (**2**,[44] 324 g, 2.04 mol) was added in small portions to 375 ml (5.19 mol) of ice-cold, stirred thionyl chloride. The clear solution was stirred for 48 hr at 4.0°. The unreacted thionyl chloride was removed by vacuum distillation at 5 mm, employing a liquid nitrogen trap and an ice bath around the distillation flask to moderate the distillation. When distillation at ambient temperature ceased (thionyl chloride removed), the liquid nitrogen trap was removed and large KOH traps were connected between the vacuum pump and distillation apparatus. A glass helices column was fitted to the distillation flask and a heating mantle was attached. The pyrolysis–distillation was begun and the fraction with bp 86–95° (5 mm) was collected. This material was redistilled to yield 100 g (35%), bp 96–100° (6 mm) [lit.[7] bp 119° (18 mm)], of 1-methyladipimide. Gas chromatography[45] showed the product to be 99.4% pure: λ_{max}^{MeOH} 235 mμ (ϵ 1580); ir (neat) 1721, 1664 cm^{-1} (C=O); nmr ($CDCl_3$) τ 6.96 (singlet, 3 H), 7.16 (distorted triplet,[46] 4 H), 8.10 (distorted triplet,[46] 4 H).

(34) (a) J. A. Elvidge, R. P. Linstead, and P. Sims, *J. Chem. Soc.*, 1793 (1953); (b) J. A. Elvidge and P. Sims, *ibid.*, *C*, 385 (1966).

(35) J. A. Elvidge and P. D. Ralph, *ibid.*, *C*, 387 (1966).

(36) W. Flitsch, *Chem. Ber.*, **97**, 1548 (1964).

(37) (a) T. Nozoe in "Non-Benzenoid Aromatic Compounds," D. Ginsburg, Ed., Interscience Publishers, New York, N. Y., 1959, Chapter VII; (b) P. Paulson, *Chem. Rev.*, **55**, 9 (1955).

(38) It has been estimated that tropone[39] and 1-methyl-2-pyridone[40a] have resonance energies of 16–24 and 12–15 kcal/mol, respectively.

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(45) Glpc analyses were carried out employing a 5-ft 20% FFAP on Chromosorb W column. Injection port and detector temperature were maintained at 290°. The column temperature was 240° and the flow rate 25 ml/min. The imide had a retention time of 5.4 min.

(46) This is a very good example of virtual coupling: see R. Silverstein and G. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1967, p 130.

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92; mol wt, 141. Found: C, 59.50; H, 7.73; N, 9.75; mol ion, 141.

Bromination of 1-Methyladipimide.—Imide **3** was brominated using the method of King and Ostrum.[8] Cupric bromide (25.7 g, 115 mmol) was ground in a mortar and pestle and placed in a 250-ml round-bottomed flask. Ethyl acetate (90 ml) was added, and the flask fitted with a condenser and magnetic stirring bar. The mixture was heated, with stirring, to reflux. The imide (3.69 g, 26.2 mmol) was dissolved in 80 ml of chloroform and also heated. The solution of the imide was added to the stirred mixture of cupric bromide. The reaction was continued at reflux for 24 hr. The reaction mixture was cooled and filtered to remove the copper salts, and the filtrate evaporated to yield a viscous black oil. The oil was dissolved in a small amount of ethyl acetate and chromatographed on 280 g of Mallinckrodt SilicAR CC-7, 100/200 mesh. Initially a solvent system of hexane–ethyl acetate 99:1 was employed, with a gradual change to 95:5 during the addition of the first liters of solvent. The remainder of the elution was done with a 95:5 solvent mixture. Two major products were collected. The fast fraction was collected, concentrated and recrystallized from hexane to yield 285 mg (3%) of colorless cubes, mp 108.5–110°, of 3,3,6-tribromo-1-methyladipimide (**5**): λ_{max}^{MeOH} 252 mμ (ε 638); ir (KBr) 1748 1692 cm^{-1} (C=O); nmr ($CDCl_3$) τ 5.18 (four lines, 1 H), 6.68, (singlet, 3 H), 6.90 (multiplet, 2 H), 7.11–7.92 (multiplet, 2 H).

Anal. Calcd for $C_7H_8NO_2Br_3$: C, 22.19; H, 2.11; N, 3.70; Br, 63.42. Found: C, 22.03; H, 2.14; N, 3.78; Br, 62.92.

The more slowly moving fraction was collected, concentrated and recrystallized slowly from hexane to yield 1.562 g (19%), colorless plates, mp 58.2–9.5°, of *trans*-3,6-dibromo-1-methyladipimide (**4**): λ_{max}^{MeOH} 245 mμ (ε 576); ir (KBr) 1727, 1672 cm^{-1} (C=O); nmr ($CDCl_3$) τ 4.90 (multiplet, 2 H), 6.73 (singlet, 3 H), 7.08–8.00 (multiplet, 4 H).

Anal. Calcd for $C_7H_9NO_2Br_2$: C, 28.09; H, 3.01; N, 4.68; Br, 53.50; mol wt, 298.898. Found: C, 28.17; H, 3.03; N, 4.68; Br, 53.62; mol ion, 298.895.

1-Methylazepine-2,7-dione (1)—Dibromoimide **4** (500 mg, 1.67 mmol) was refluxed with 200 ml of triethylamine for 6 hr. The reflux apparatus was placed in an oil bath maintained at 120°. After completion of the reaction, the reaction mixture was cooled to ambient temperature, filtered to remove the triethylamine hydrobromide and the filtrate evaporated to yield a light yellow oil. This oil was chromatographed on five 0.5-mm silica plates, employing a solvent system of hexane–ethyl acetate 60:40. These plates exhibited two major bands, R_f 0.58 and 0.95, corresponding to the azepinedione and unreacted dibromoimide, respectively. The band at R_f 0.58 was collected and stirred for 1 hr with a mixture of ethyl acetate–chloroform 75:25. The silica was filtered off and the filtrate evaporated. The evaporate was recrystallized from hexane to yield 60 mg (26%, colorless needles, mp 76–77.8°) of 1-methylazepine-2,7-dione: λ_{max}^{MeOH} 220 mμ (ε 15,200), 287 (3620); ir (KBr) 1658, 1595 cm^{-1} (C=O); nmr (C_6D_6) τ 3.65, 4.21 (AA'BB', 4 H), 6.58 (singlet, 3 H). Mass spectrum (70 eV) *m/e* (relative intensity) 137 (35), 109 (38), 108 (100), 96 (22), 82 (11), 81 (82), 80 (60), 55 (13), 54 (13), 53 (22), 52 (76), 51 (70), 50 (30), (only absorbances with relative intensities greater than 10% are listed).

Anal. Calcd for $C_7H_7NO_2$: C, 61.31; H, 5.14; N, 10.21; mol wt, 137. Found: C, 61.00; H, 4.81; N, 9.95; mol ion, 137.

Reaction of 1-Methylazepine-2,7-dione with Bromine.—Azepinedione **1** (65 mg, 0.474 mmol) was dissolved in 250 ml of hexane (Baker, Chromatography Grade) and the flask containing the solution covered with aluminum foil and immersed in an ice bath. Freshly prepared 10% (v/v) bromine (6 ml) in hexane solution was added, and the resulting solution stirred for 64 hr at 0°. The reaction mixture was rotary evaporated at 0° under 1 mm pressure. The crystalline residue was recrystallized from petroleum ether. All operations except for the recrystallization were carried out in the dark to prevent decomposition of the product to the starting material. This reaction yielded 90 mg (64%), colorless plates, mp 78–79°, of *trans*-5,6-dihydro-5,6-dibromo-1-methylazepine-2,7-dione (**8**): λ_{max}^{MeOH} 215 mμ (ε 10,400), 245 (6500); ir (KBr) 1706, 1635 cm^{-1} (C=O); nmr (C_6D_6) τ 4.00 (doublet, J = 12.1 Hz, 1 H), 4.55 (doublet of doublet of doublets, J = 12.1, 7.0, 1.4 Hz, 1 H), 5.32 (doublet of doublets, J = 5.0, 1.4 Hz, 1 H), 6.25 (doublet of doublets, J = 7.0, 5.0 Hz, 1 H), 6.90 (singlet, 3 H).

Anal. Calcd for $C_7H_7NO_2Br_2$: C, 28.30; H, 2.36; N, 4.72; Br, 53.87; mol wt, 297. Found: C, 28.36; H, 2.64; N, 4.62; Br, 54.46; mol ion, 297.

Reaction of 1-Methylazepine-2,7-dione with Cyclopentadiene.—To 52 mg (0.38 mmol) of **1** was added 3 ml (37.2 mmol) of freshly prepared cyclopentadiene. The colorless solution was stirred for 3 hr. Thin layer chromatography on 0.75-mm silica plates, employing a solvent system of hexane–ethyl acetate, 70:30, revealed three major bands: R_f 0.60, 0.40, 0.20. The band at R_f 0.20 corresponded to unreacted azepinedione. The reaction mixture was separated on five 0.75 mm plates, the bands collected, extracted with ethyl acetate–chloroform, filtered and the filtrate evaporated. Band R_f 0.60 was recrystallized from petroleum ether to yield 40 mg (52%), colorless plates, mp 70.5–71.5°, of *exo*-4-methyl-4-azatricyclo[7.2.1.0^{2,8}]dodeca-6,10-diene-3,5-dione (**10**): λ_{max}^{MeOH} 220 mμ (ε 6960); ir (KBr) 1712, 1664 cm^{-1} (C=O); nmr ($CDCl_3$) τ 3.63 (multiplet, H_6,H_7, 2 H), 4.29 (multiplet, H_{10},H_{11}, 2 H), 6.16 (multiplet, H_1,H_9, 2 H), 6.40–6.97 (multiplet, H_2,H_8, 2 H), 6.87 (singlet, 3 H), 7.30 (multiplet, H_{12s}, 1 H), 7.95 (multiplet, H_{12a}, 1 H).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89; mol wt, 203. Found: C, 71.09; H, 6.36; N, 6.89; mol ion, 203.

After extraction, the slower band was dried over Linde Molecular Seive 4X. After drying there remained 3.4 mg (4.4%), colorless liquid, of *endo*-4-methyl-4-azatricyclo[7.2.1.0^{2,8}]dodeca-6,10-diene-3,5-dione (**11**): λ_{max}^{MeOH} 220 mμ (ε 6500); ir ($CHCl_3$) 1712, 1664 cm^{-1} (C=O); nmr ($CDCl_3$) τ 3.49–4.50 (multiplet, H_6,H_7,H_{10},H_{11}, 4 H), 6.20–7.00 (multiplet, H_1,H_9,H_2,H_8, N–CH_3, 7H), 8.50 (multiplet, H_{12a}, H_{12s}, 2H).

Anal. Calcd for $C_{12}H_{13}NO_2$: mol wt. 203.094. Found: mol ion, 203.097.

Ethanolysis of 1-Methylazepine-2,7-dione.—Azepinedione **1**, 50 mg (0.36 mmol), was stirred in the dark, with 150 ml of absolute ethanol and 9 ml of a 1×10^{-5} *M* NaOH/EtOH solution for 3 weeks at ambient temperature. The reaction mixture was evaporated and chromatographed on six 0.75-mm silica plates employing a solvent system of ethyl acetate–hexane 55:45. The plates exhibited only two bands, R_f 0.60 and 0.40, corresponding to the unreacted azepinedione and the ethanolic product, respectively. The band at R_f 0.40 was collected, extracted with ethyl acetate–chloroform and the extract was recrystallized from hexane to yield 20 mg (30%), colorless needles, mp 80.5–82.0°, of ethyl N-methyl-*cis*,*cis*-muconamate (**7**): λ_{max}^{EtOH} 267 mμ (ε 24,700); ir (KBr) 3311 (N–H), 1718 (C=O, ester), 1645 (C=O, amide), 1592 (C=C), 1555 cm^{-1} (NH); nmr (C_6D_6) τ 1.57 (six-line multiplet, Hβ, 2 H), 4.30 (four-line multiplet, Hα, 2 H), 6.00 (quartet, J = 7.1 Hz, 2 H), 7.59 (doublet, J = 4.5 Hz, 3 H), 9.04 (triplet, J = 7.1 Hz, 3 H).

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65; mol wt, 183. Found: C, 59.07; H, 7.16; N, 7.52; mol ion, 183.

Ethyl N-Methyladipamate (12).—N-Methyladipamic acid (**2**, 10 g, 63 mmol) was stirred with 350 ml of absolute ethanol while dry HCl was bubbled into the reaction flask. After 28 hr the reaction mixture was evaporated to an oil, dissolved in water and neutralized with solid $NaHCO_3$. The aqueous solution was extracted with ether, and the extracts were combined and dried over anhydrous Na_2SO_4. The ether was distilled off and the liquid distilled under vacuum to yield 4.53 g (39%), colorless liquid, bp 140° (0.7 mm), of ethyl N-methyl adipamate: ir ($CHCl_3$) 3279 (NH) 1736 (C=O, ester), 1675 (C=O, amide), 1538 cm^{-1} (NH); nmr ($CDCl_3$) τ 2.30 (broad singlet, 1 H), 5.83 (quartet, J = 7.4 Hz, 2 H), 7.21 (doublet, J = 4.9 Hz, 3 H), 7.66 (multiplet, 4 H), 8.28 (multiplet, 4 H), 8.74 (triplet, J = 7.4 Hz, 3 H).

Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48; mol wt, 187. Found: C, 58.17; H, 9.43; N, 7.73; mol ion, 187.

Hydrogenation of Ethyl N-Methyl-*cis*,*cis*-muconamate (7).—Hydrogenation was accomplished with a (Brown)[2] Micro Hydro-Analyzer[47a] which generated a very active platinum on carbon catalyst *in situ*. Muconamate **7** (8 mg, 0.043 mmol) was hydrogenated according to the normal procedure,[47b] except that the quantities for catalyst generation were doubled, and those for hydrogen generation were tripled. The reaction mixture was filtered, evaporated, and triturated with chloroform and the chloroform solution reduced to about 1 ml. The mixture was separated by preparative gas chromatography.[48] The chromato-

(47) (a) Delmar Scientific Laboratories, Maywood, Ill. (b) "Operating Instructions for the (Brown)[2] Micro Hydro-Analyzer," Delmar Scientific Laboratories, Maywood, Ill., 1964.

(48) A 10-ft silicon grease on Haloport F column was employed at a temperature of 210° and a flow rate of 30 ml/min. Ethyl N-methyladipamate had a retention time of 4.4 min.

gram exhibited two peaks, retention times 1.2 and 4.4 min, corresponding to the solvents and the hydrogenation product, respectively. The peak at 4.4 min was collected and rechromatographed to yield a small amount of a colorless liquid. This liquid had an infrared spectra ($CHCl_3$) identical with that of previously prepared ethyl N-methyl adipamate (12).

Registry No.—**1**, 19519-85-8; **3**, 19519-86-9; **4**, 19519-87-0; **5**, 19519-88-1; **7**, 19519-89-2; **8**, 19519-90-5; **10**, 19519-91-6; **11**, 19519-92-7; **12**, 19519-93-8.

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Addition of Dienophiles to the Acridizinium Ion. III.[1] Evidence for a Two-Step Reaction

C. K. BRADSHER AND J. A. STONE[2]

Department of Chemistry, Duke University, Durham, North Carolina 27706
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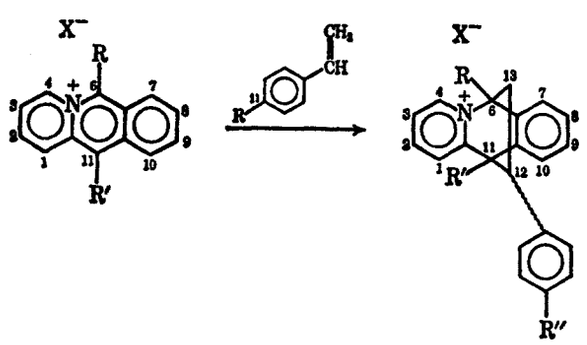
The introduction of a methyl group into the two *meso* positions of the acridizinium ion has opposite effects, at position 6 *decreasing* and at position 11 *increasing* the rate of reaction. Even in the presence of sodium acetate (hence in the absence of any traces of perchloric acid) diethyl maleate adds to acridizinium ion to give a rearranged (*anti, syn*) product (12). It is believed that these observations can best be explained in terms of a two-step mechanism.

The discovery several years ago[3] that the acridizinium (benzo[*b*]quinolizinium) ion (1) will undergo 1,4 cycloaddition with some common dienophiles was rationalized by the recent evidence[4,5] that the reaction is an example of what Sauer and Wiest have designated as a Diels–Alder reaction with inverse electron demand

SCHEME I



1, R = R′ = H
2, R = CH_3; R′ = H
3, R = H; R′ = CH_3
4, R = R′ = CH_3
5, R = R′ = H
6, R = CH_3; R′ = H
7, R = H; R′ = CH_3
8, R = R′ = CH_3

(Scheme I).[6] The great ease with which acridizinium derivatives can be prepared[7–9] makes the system of unique promise in the study of the factors affecting the Sauer and Wiest type of cycloaddition.

For the classical Diels–Alder reaction, it has been reported that introduction of methyl groups into the *meso* (9,10) positions of anthracene results in a very significant enhancement of the reaction rate.[10] Difficulty in assessing the relative importance of steric and electronic factors might have made prediction of the net effect of *meso* substitution difficult, but the observed rate enhancement is readily understood in terms of the predominant effect of the electron release of the methyl groups.

If one introduces one or two methyl groups into the *meso* (6, 11) positions of the acridizinium ion, it would appear, at least at first glance, that both steric and electronic effects would cooperate to reduce the speed of the reaction. With 6-methylacridizinium (2) perchlorate, the rate of addition of styrene to form adduct **6**, as measured by the disappearance of the long-wavelength absorption of the 6-methylacridizinium ion, is in fact about one-half the rate at which the acridizinium ion undergoes the same reaction (Table I). The nmr of styrene adduct **6** showed the signal for the C-11 proton as a doublet, indicating that the phenyl group was at the 12 rather than the 13 position. The adducts from the reaction of 6-methylacridizinium ion with the *substituted* styrenes were not isolated, but it was observed that the effect of the *para* substituent in the styrene ring on the rate parallels that observed[5] earlier for the acridizinium ion.

If the methyl group is introduced at position 11 instead of position 6 there is no decrease in the observed rate of addition to styrene, but instead a 13-fold *increase* in reaction rate over that for the unsubstituted acridizinium ion. A similar but smaller increase in rate was observed when methyl groups were introduced in both the 6 and 11 positions of the acridizinium ion. The adducts of styrene with 11-methyl- and 6,11-dimethylacridizinium ion (**7** and **8**) cannot be characterized as 12-phenyl (rather than 13-phenyl) derivatives with the same certainty as the adduct which possesses a hydrogen at position 11[11]; however, all indirect

(1) For the preceding papers of this series, see ref 3 and 5.
(2) NASA Trainee. This work was supported in part by Public Health Grant No. HE-02170 of the National Heart Institute of the National Institutes of Health.
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(9) C. K. Bradsher and J. C. Parham, *J. Heterocycl. Chem.*, **1**, 121 (1964).
(10) Preparative experiments carried out by W. E. Bachmann and M. C. Kloetzel [*J. Amer. Chem. Soc.*, **60**, 481 (1938)] indicated that 9,10-dimethylanthracene might react as much as 90 times as fast as anthracene.
(11) Even in the cases in which there is a hydrogen at position 6, it is so strongly deshielded by the adjacent positive charge that the signal from it becomes indistinguishable from the signals from the aromatic protons.