π-Equivalent Heterocyclic Congeners of Tropone. Azatropones[1]

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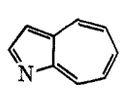
Seven azatropones, π-equivalent heterocyclic congeners of tropone, have been prepared and characterized. Thus treatment of 4,7-dimethyl- (**10**), 4,6,7-trimethyl- (**12**), and 3,4,6,7-tetramethyl-1*H*-azepine-2,5-dione (**14**) with triethyloxonium fluoborate afforded respectively, 7-ethoxy-2,5-dimethyl-4*H*-azepin-4-one (**19**), 5-ethoxy-4,6,7-trimethyl-2*H*-azepin-2-one (**22**), and 5-ethoxy-3,4,6,7-tetramethyl-2*H*-azepin-2-one (**28**). With the same reagent, 1*H*-benz[*f*]azepine-2,5-dione (**16**) and 5*H*-morphanthridine-6,11-dione (**18**) gave 2-ethoxy-5*H*-benz[*f*]azepin-5-one (**34**) and 11-ethoxybenz[*c*]cyclohexadienyl[5,6-*f*]-2*H*-azepin-2-one (**42**), respectively. Trimethyloxonium fluoborate also converted **12** and **14** to their respective azatropones, 5-methoxy-4,6,7-trimethyl- (**26**) and 5-methoxy-3,4,6,7-tetramethyl-2*H*-azepin-2-one (**31**). Proof of structure of 4-azatropones, **19** and **34**, and 2-azatropones, **22**, **26**, **28**, **31**, and **42**, is provided and mechanisms for their formation are suggested. Nmr data show no evidence of a ring current in any of these azatropones, and the ease with which they are both hydrogenated and/or hydrolyzed indicates no special aromatic stabilization.

General syntheses of π-equivalent[3] azacyclic congeners of azulene (10π) and cyclooctatetraene (8π) have been realized with the preparation of azaazulene (**1**)[4] and 2-alkoxyazocines (**2**).[5]



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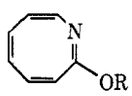

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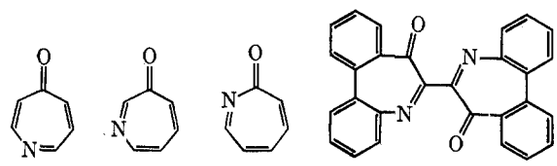
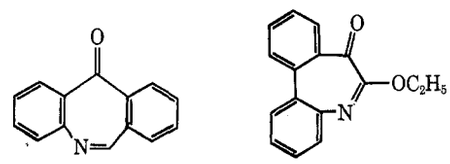
Synthetic pathways devised to prepare azatropones (**3**–**5**), the monocyclic 6π-equivalent heterocyclic congeners of tropone, and their annelated derivatives has been strewn with failure,[6-10] error,[11-15] and limited success (**6**–**8**).[13,14]

An avowed purpose for all these preparations of (4*n* + 2)π-equivalent heterocyclic conjugated systems is their characterization by nmr spectroscopy to determine the degree of π-electron delocalization. Extensive charge delocalization (aromaticity) would be reflected in an appreciable induced ring current which in turn would be revealed by substantial deshielding of vinyl protons and methyl substituents on the azatropone ring system.



3 **4** **5** **6**



7 **8**

Azatropones **6** and **8** have neither of these substituents, while the vinyl proton singlet (δ 8.81) in **7** is adjacent to both nitrogen and the fused aromatic ring and its downfield position could alternatively be explained by conventional deshielding effects and not a ring current.

This paper describes a convenient, two-step synthesis of substituted and annelated azatropones and reports on a study of their chemical and physical properties which provides sufficient evidence for a conclusion regarding their aromaticity.

Thus, the observed ring expansion of alkyl-1,4-benzo-, 1,4-naphtho-, and 9,10-anthraquinones to 2,5-azepinediones under Schmidt reaction conditions[16-19] coupled with the extraordinary propensity of Meerwein's reagent, trialkyloxonium fluoborate, to selectivity O-alkylate amides,[20] afforded a direct route to the synthesis of 4*H*-azepin-4-ones (type **3**) and 2*H*-azepin-2-ones (type **5**).

Treatment of 2,5-dimethyl- (**9**), 2,3,5-trimethyl- (**11**), and 2,3,5,6-tetramethyl-1,4-benzoquinone (**13**) with sodium azide in concentrated sulfuric acid gave 4,7-dimethyl- (**10**, 66%), 4,6,7-trimethyl- (**12**, 70%), and 3,4,6,7-tetramethyl-1*H*-azepine-2,5-dione (**14**, 79%), respectively.[16-18] Similarly 1,4-naphthoquinone (**15**) and anthraquinone (**17**) afforded the corresponding 1*H*-benz[*f*]azepine-2,5-dione (**16**, 65%)[20] and 5*H*-morphanthridine-6,11-dione (**18**, 86%)[19] (Scheme I).

Azatropones (Schemes II and III).—The reaction of **10** with triethyloxonium fluoborate[20] in methylene chloride afforded the azatropone 7-ethoxy-2,5-dimethyl-

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(3) A. G. Anderson, Jr., W. F. Harrison, and R. G. Anderson, *J. Amer. Chem. Soc.*, **85**, 3448 (1963).

(4) T. Nozoe, S. Seto, S. Matsumara, and T. Terawasa, *Chem. Ind. (London)*, 1356, 1357 (1954); P. A. Pauson, *Chem. Rev.*, **55**, 9 (1955).

(5) L. A. Paquette, T. Kakihana, J. F. Hansen, and J. C. Philips, *J. Amer. Chem. Soc.*, **93**, 152 (1971), and succeeding papers.

(6) J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 4174 (1957); 3377 (1958).

(7) G. R. Proctor and R. H. Thompson, *ibid.*, 2302 (1957).

(8) A. Cromarty and G. R. Proctor, *Chem. Commun.*, 842 (1968).

(9) N. A. Evans, R. B. Johns, and K. R. Markham, *Aust. J. Chem.*, **20**, 713 (1967).

(10) M. A. Rehman, *J. Nat. Sci. Math.*, **9**, (2), 297 (1969); *Chem. Abstr.*, **73**, 344 (87764*f*) (1970).

(11) G. R. Proctor, *Chem. Ind. (London)*, 408 (1960).

(12) W. R. Paterson and G. R. Proctor, *J. Chem. Soc.*, 3468 (1962).

(13) R. G. Cooke and I. M. Russell, *Tetrahedron Lett.*, 4587 (1968).

(14) W. C. Peaston and G. R. Proctor, *J. Chem. Soc.*, 2481 (1968).

(15) E. Bullock, B. Gregory, and A. W. Johnson, *J. Amer. Chem. Soc.*, **84**, 2260 (1962); E. Bullock, B. Gregory, A. W. Johnson, P. J. Brignell, U. Eisner, and H. Williams, *Proc. Chem. Soc.*, 122 (1962); E. Bullock, B. Gregory, and A. W. Johnson, *J. Chem. Soc.*, 1632 (1964).

(16) D. Misiti, H. Moore, and K. Folkers, *Tetrahedron*, **22**, 1201 (1966).

(17) R. W. Richards and R. M. Smith, *Tetrahedron Lett.*, 2361 (1966).

(18) G. R. Bedford, G. Jones, and B. R. Webster, *ibid.*, 2367 (1966).

(19) M. M. Coombs, *J. Chem. Soc.*, 4200 (1958).

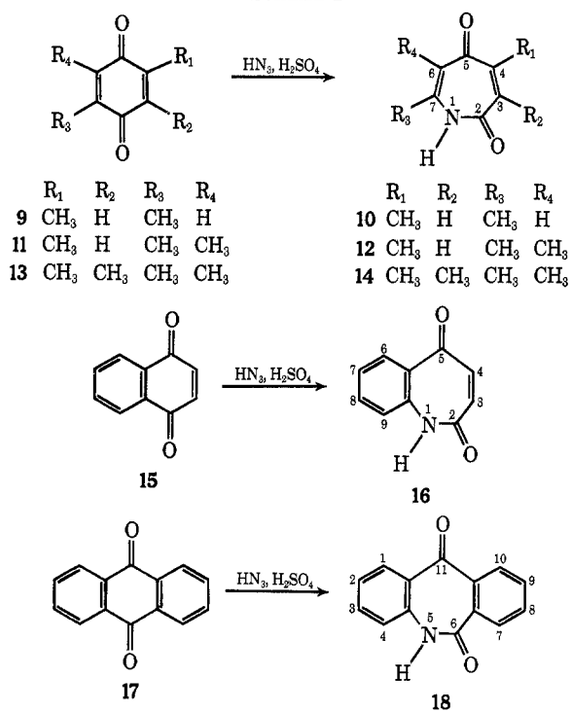
(20) H. Meerwein, *Org. Syn.*, **46**, 113, 120 (1966).

TABLE I

NMR, IR, AND UV SPECTRAL DATA FOR AZATROPONES

Azatropone	Nmr (δ) =CCH3 Chemical shift	Multiplicity	Coupling constant, Hz	=CH Chemical shift	Multiplicity	Coupling constant, Hz	Ir $\lambda_{max}^{KBr-film}$, cm^{-1} (μ) C=O	=COC	Uv λ_{max}^{EtOH}, nm (ε)
19	2.20	s		6.70	q	J = 1	1620 (6.17)	1230 (8.13)	225 (26,500)
	2.08	q	J = 1	6.13	s				300 (7,100)
22	2.30	q	J = 0.5	6.68	q	J = 1	1640 (6.10)	1275 (7.85)	225 (25,000)
	2.20	d	J = 1						310 (7,700)
	2.08	q	J = 0.5						
26	2.30	q	J = 0.5	6.68	q	J = 1	1640 (6.10)	1270 (7.88)	225 (21,000)
	2.20	d	J = 1						310 (6,000)
	2.10	q	J = 0.5						
28	2.13	q	J = 0.5				1625 (6.15)	1285 (7.78)	230 (22,000)
	2.10 (6 H)	s							320 (7,300)
	1.97	q	J = 0.5						
31	2.13	q	J = 0.5				1620 (6.17)	1295 (7.72)	230 (20,000)
	2.10 (6 H)	s							320 (5,100)
	1.97	q	J = 0.5						
34				6.81	q (AB)	J = 12	1610 (6.21)	1220 (8.20)	218 (38,000)
				6.65	q (AB)	J = 12			265 (10,600)
42							1660 (6.02)	1275 (7.85)	233 (32,500)

SCHEME I



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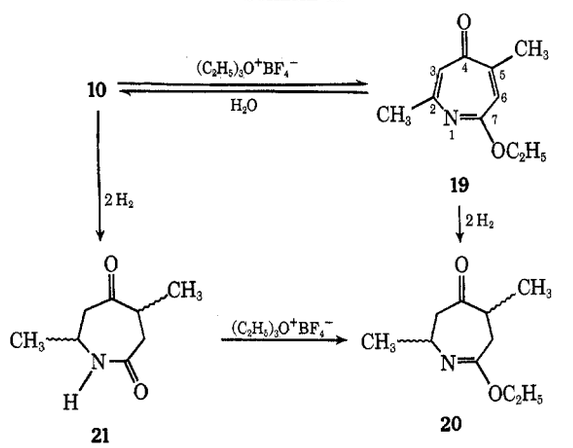


4*H*-azepin-4-one (**19**, 4%) (Scheme II). Alkylation of **12** and **14** with the same reagent, however, gave 5-ethoxy-4,6,7-trimethyl-2*H*-azepin-2-one (**22**, 63%) and 5-ethoxy-3,4,6,7-tetramethyl-2*H*-azepin-2-one (**28**, 70%), respectively (Scheme III). The 4-azatropone **19** can be envisioned as arising from O-alkylation of the enol of **10**, while vinylogous lactam–lactim tautomerism of **12** and **14** followed by O-alkylation[21] may account for **22** and **28**.

Trimethyloxonium fluoborate[20] converted **12** and **14** to 5-methoxy-4,6,7-trimethyl- (**26**, 51%) and 5-methoxy-3,4,6,7-tetramethyl-2*H*-azepin-2-one (**31**, 63%), respectively. Although the purpose of making the OCH_3 derivatives was to simplify the nmr spectrum of these azatropones, the nmr spectra of **22** and **28** were analogous to **26** and **31**, respectively (apart from the OR group), and the corresponding uv spectra were virtually superimposable.

Differences in preparative procedure (*vide infra*), the dramatic difference in yields, and subtle differences in pertinent spectral data (tabulated in Table I) initially delineated but did not distinguish the 4-azatropone **19** from 2-azatropones **22** (**26**) and **28** (**31**).

Structure Proof of 19, 22, and 28.—Hydrogenation of **19** over 5% Pd/C at atmospheric pressure resulted in an uptake of 2 mol equiv of hydrogen and afforded a distillable oil. The vinyl protons were absent from the nmr spectrum of this reduction product and the methyl groups were aliphatic doublets. The ir spectrum displayed a new carbonyl band at 1775 cm^{-1} (5.63 μ) and gave no evidence of NH absorption. Only end absorption was observed in the uv, and vpc indicated a two-component mixture. The spectral and analytical evidence was consistent with a stereoisomeric mixture of 7-ethoxy-2,5-dimethyl-2,3,5,6-tetrahydro-4*H*-azepin-4-one (**20**, obtainable only from **19**). Hydrogenation of **10** over 30% Pd/C afforded a white

(21) N-Methylation of **14** was achieved by treatment of a solution of **14** in DMF with sodium hydride and methyl iodide. The distinguishing feature of the nmr spectrum of product 1,3,4,6,7-pentamethyl-1*H*-azepine-2,5-dione (**33**, 86%) was a new methyl proton singlet at δ 3.17. This is consistent with a methyl group on N and not O: *cf.* **33** with **26** and **31**. Refluxing **14** with dimethyl sulfate in benzene for 24 hr led only to the recovery of starting material.

product (**21**) whose spectral data indicated a keto compound with substantial enol tautomerism. Alkylation of **21** with triethyloxonium fluoborate gave the identical mixture of stereoisomeric O-alkylated imino ethers (**20**) obtained from hydrogenation of **19**. As with tropone,[22] **19** failed to give a 2,4-DNPH derivative.

Hydrogenation of **22** at ambient temperature and atmospheric pressure ceased after 1 mol equiv of hydrogen had been absorbed.[23] The product nmr spectrum indicated that hydrogenation of the sterically less hindered double bond had occurred and suggested structure **23**, 5-ethoxy-4,6,7-trimethyl-3,4-dihydro-1*H*-azepin-2-one. Thus we attribute the 3 H multiplet (δ 2.68–2.22) to the CH_2 protons (sharp multiplet centered at δ 2.47) adjacent to the C=O, superimposed upon a broad allyl CH resonance which extends the multiplet upfield to δ 2.22.[24]

Column chromatography of **23** led *via* hydrolysis of the labile vinyl ether function to the keto–amide tautomer 4,6,7-trimethyl-2,3,4,5-tetrahydro-1*H*-azepine-2,5-dione (**24**, 72%). The structure of **24** was confirmed by successive hydrogenation (1 mol equiv) of **12** followed by column chromatography to **24** (71%). Alkylation of **24** prepared in this manner with triethyloxonium fluoborate afforded **23** (23%). Compounds **23** and **24** prepared by these alternative methods were identical by all the usual criteria.

Careful reduction (30% Pd/C) of **26** with 3 mol equiv of hydrogen led to a mixture of 5-methoxy-4,6,7-trimethylhexahydro-1*H*-azepin-2-ones (**27**, 65%); four isomers of **27** could be distinguished by vpc and nmr spectroscopy.

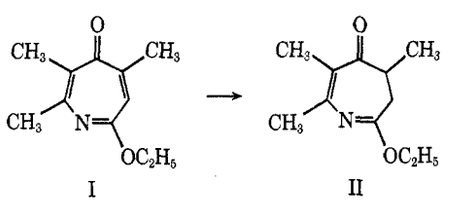
Since acid-catalyzed hydrolysis of **22** and **26** quantitatively converted them to **12**, it is not surprising that treatment of **22** and **26** with 2,4-DNPH under acidic conditions gave a hydrazone **25** identical in all respects with that obtained directly from **12**.

Hydrogenation (30% Pd/C) of **28** afforded an unstable, white, crystalline powder (22%) which could be recrystallized and purified only with substantial loss of product. In the nmr, the recrystallized material displayed three methyl singlets (δ 2.10, 1.90, and 1.65), a relatively shielded methyl doublet (δ 1.16), an NH proton (δ 6.50), and an alicyclic ring proton (δ 2.67). Since this latter proton does not seem to appear sufficiently downfield to be adjacent to nitrogen, the hydrogenation product was structured as **32** which would result from conventional hydrogenation of the double bond at $\Delta^{3,4}$ (**28** → **29**) followed by a 1,5-sigmatropic hydrogen shift to **32**. The π–π^* transition of **32** [λ_{max} 223 nm (ϵ 8800)] is intermediate between and less probable than in the nonconjugated acetamide [λ_{max} 179 nm (ϵ 9500)] and the highly conjugated acetanilide [λ_{max} 238 nm (ϵ 10,500)].[27,28]

Acid-catalyzed hydrolysis of **28** and **31** resulted in quantitative conversion to **14**. Thus, treatment of **14**, **28**, and **31** with 2,4-DNPH under acidic conditions led to the same hydrazone **30**.

Benz-Fused Azatropones (Schemes IV and V).—The spectral and chemical properties of Schmidt rearrangement product **16** were similar to 7,8-dimethyl-1*H*-benz[*f*]azepine-2,5-dione (**38**) prepared by bromination–dehydrobromination of 7,8-dimethyl-3,4-dihydro-1*H*-benz[*f*]azepine-2,5-dione (**39**).[30] Treatment of **16** with triethyloxonium fluoborate transformed it to 2-ethoxy-5*H*-benz[*f*]azepin-5-one (**34**, 6.5%) with no recovery of starting material. In the nmr, the presence of an aromatic peri proton doublet at δ 8.08 coupled to both ortho- and meta-ring protons was sufficient to assign azatropone structure **34** to this O-alkylation product.

In an attempted synthesis of an azatropolone, Rees[30] had converted **39** to 7,8-dimethyl-2,3,4,5-tetrahydro-1*H*-benz[*f*]azepine-2,4,5-trione (**41**) *via* anil **40**. The insolubility of **41** precluded spectral studies in solution but the very limited chemical evidence available excluded heterotropolone behavior in **41**. The availability of **16** permitted a preparation of the unsubstituted trione **37**. Thus, hydrogenation of **16** (Pd/C) afforded 3,4-dihydro-1*H*-benz[*f*]azepine-2,5-dione (**35**, 86%). Base-catalyzed condensation of **35** with *N*,*N*-dimethyl-*p*-nitrosoaniline led to the bright red anil **36** (50%); acid hydrolysis of **36** gave yellow-green 2,3,4,5-tetrahydro-1*H*-benz[*f*]azepine-2,4,5-trione (**37**, 11%) which was insoluble in all the usual organic solvents. The carbonyl region in the infrared spectra of **37** (KBr) and



I II

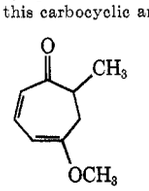
(22) H. J. Dauben, Jr., and H. J. Ringold, *J. Amer. Chem. Soc.*, **73**, 876 (1951).

(23) Reduction under more vigorous conditions led to hydrogenolysis of the labile ethoxy group.

(24) The alternative azatropone structure I on similar reduction with 1 mol equiv of hydrogen would give II whose CH proton adjacent to C=O would normally appear at distinctly lower field from the allyl CH_2 resonance. Precedent[25,26] and the position of the CH proton resonance in **20** and **24** support this view.

(25) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N. Y., 1967, p 137.

(26) O. L. Chapman, D. J. Pasto, and A. A. Griswold, *J. Amer. Chem. Soc.*, **84**, 1216 (1962), have prepared the dihydro tropone III. The CH proton adjacent to C=O in this carbocyclic analog of II indeed appears as

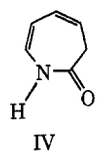


III

a multiplet skewed distinctly downfield (δ 2.91–2.25) from the (sharp) allyl CH_2 resonance (δ 2.44). The large difference in λ_{max} for **23** [300 nm (ϵ 10,000)] and III [331 nm (ϵ 7160)] also supports the presence of different chromophores in these two systems. We are grateful to Professor Chapman for a Xerox copy of this portion of the nmr spectrum which was absent in the cited paper.

(27) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, pp 9, 18.

(28) The completely unsubstituted analog IV of **32** has been prepared in



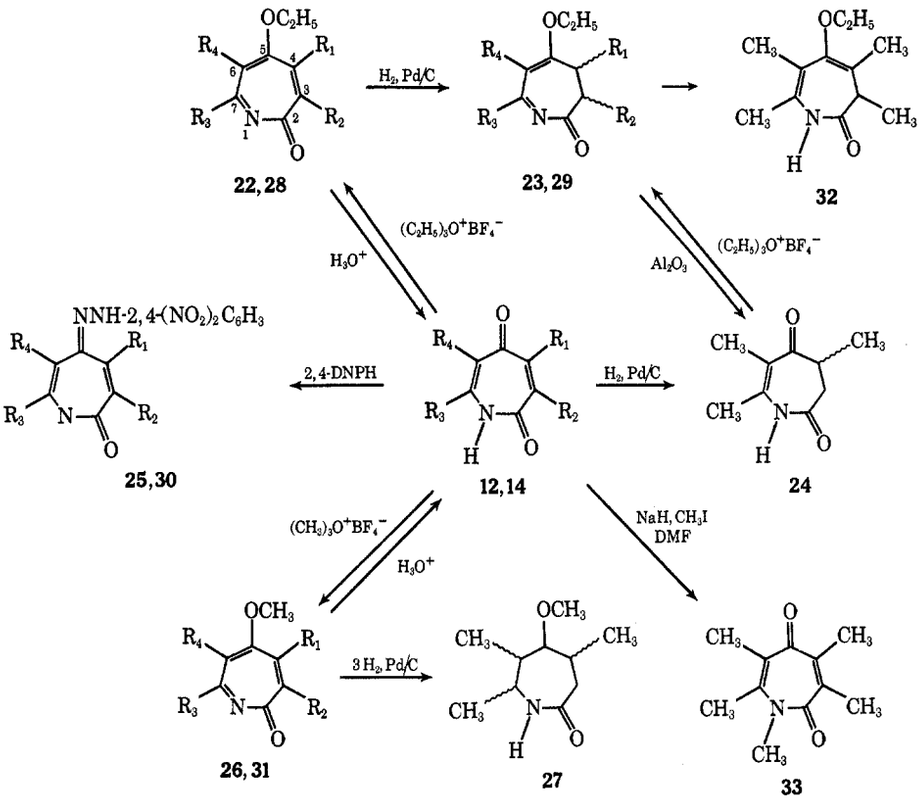
IV

which the π–π^* transition occurs below 210 nm and whose n–π^* absorption appears at 258 nm (log ϵ 3.7).[29] Dihydroazepin-2-one **32** displayed a λ_{max} 285 nm (log ϵ 3.72) in which normal alkyl substitution effects would contribute to the observed bathochromic shift.

(29) E. Vogel, R. Erb, G. Lenz, and A. Bothner-by, *Justus Liebigs Ann. Chem.*, **682**, 1 (1965).

(30) Prepared in a six-step synthesis from *o*-xylene: A. H. Rees, *J. Chem. Soc.*, 3111 (1959).

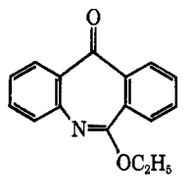
SCHEME III



12, 22-26, $R_1 = R_3 = R_4 = CH_3$; $R_2 = H$
14, 28-31, $R_1 = R_2 = R_3 = R_4 = CH_3$

41 (Nujol) were almost identical, suggesting the absence also of any enol tautomer of **37**.

Alkylation of **18** with triethyloxonium fluoborate proceeded experimentally in a manner analogous to **12** and **14** and afforded a single O-alkylation product (71%). The choice between the assigned structure **42** (11-ethoxybenz[*c*]cyclohexadienyl[5,6-*f*]-2*H*-azepin-2-one) and the alternative **42a** was based on the following evidence: (1) the absence of any deshielded



42a

aromatic peri protons in the nmr spectrum of **42**; (2) reduction of **42** with excess $NaBH_4$ did not give the tetrahydro amine anticipated from **42a**,[31] but led instead to the dihydro product 11-ethoxy-6-hydroxybenz-[*c*]cyclohexadienyl[5,6-*f*]-2*H*-azepine (**43**), (3) acid hydrolysis of **43** afforded the unknown 6-hydroxy-5,6-dihydro-11-morphanthridinone (**44**) whose physical properties [mp 247–249°; ir 1660 cm^{-1} (6.20 μ) (C=O); nmr δ 6.01 (OH) and 5.60 (CH)] clearly distinguish it from the known, isomeric 11-hydroxy-6(5*H*)-morphanthridone (**45**)[32] [mp 138–139°; ir 1740 cm^{-1} (5.75 μ) (C=O); nmr δ 3.82 (OH) and 6.50 (CH)], prepared *via* the Meerwein–Ponndorf–Verley reduction of **18**. Isomer **45** would have been the expected product had the reduction and hydrolysis sequence (**42** → **43** → **44**) commenced with **42a**. Acid hydrolysis of **42** afforded **18**, and, not unexpectedly, treatment of **18** and **42** with 2,4-DNPH under acidic conditions gave the same hydrazone **47**.

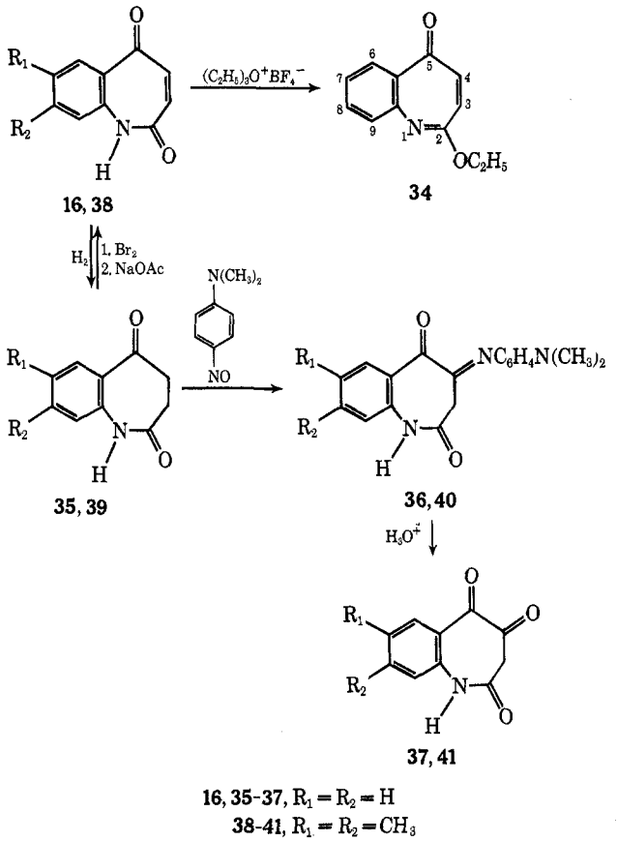
Of spectral interest was the dialkylated product obtained from the reaction of **45** with either equimolar or excess triethyloxonium fluoborate. Distillation of the viscous reaction product afforded a small amount of 11-ethoxy-5-ethyl-6-morphanthridinone (**46**, 11%) characterized by microanalytical and spectral data. The CH_2 group directly attached to the nitrogen appears as a mound in the nmr (30°) centered at δ 3.41. Progressive resolution of the mound occurred as the temperature was raised until, at 75°, it became a fairly sharp quartet. This temperature dependency is attributed to slow nitrogen inversion at low temperature with the nmr spectrum at 30° recording the coalescence point.

Aromaticity.—The position of ring protons (δ 6.13–6.81) and methyl groups (δ 1.97–2.30) in the nmr of 4-azatropones **19** and **34** and 2-azatropones **22**, **26**, **28**, and **31** remain well within the vinyl region and were not significantly shifted to lower fields relative to their respective precursor azepinediones. Thus there is no nmr evidence to support the postulation of a ring current. Finally, the ease with which all these azatropones could be both hydrogenated and/or hydrolyzed leads us to the inescapable conclusion that these azatropones have no special "aromatic" stabilization.

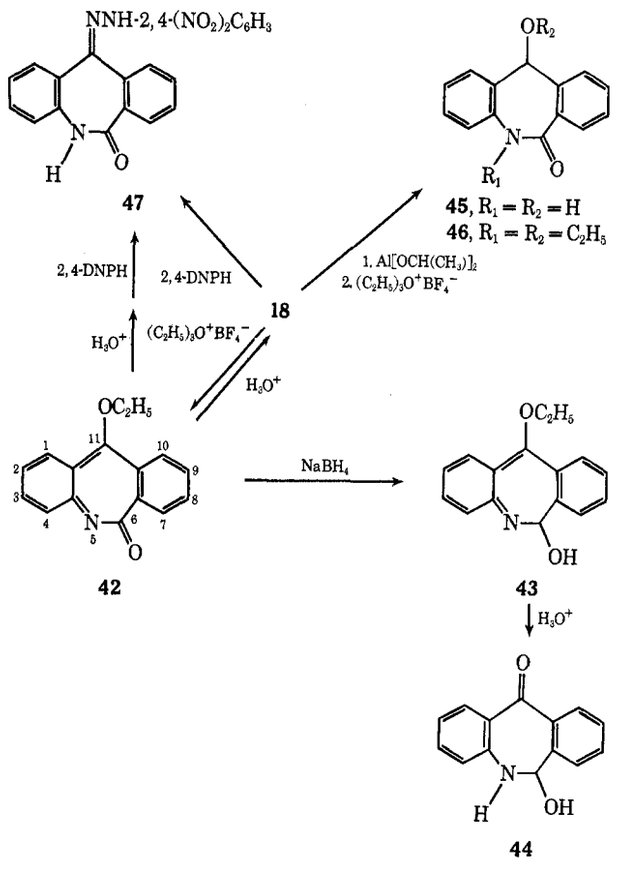
(31) R. F. Borsch, *Tetrahedron Lett.*, 61 (1968).

(32) *Chem. Abstr.*, **62**, 10422 (1965); J. O. Jilek, J. Pomykacek, E. Luatek, V. Seidlova, M. Rajsner, K. Pelz, B. Hoch, and M. Protivia, *Collect. Czech. Chem. Commun.*, **30** (2), 445 (1965) [*Chem. Abstr.*, **63**, 4257 (1965)].

SCHEME IV



SCHEME V



Experimental Section[33]

Schmidt Reaction.—**4,7-Dimethyl-** (10), **4,6,7-trimethyl-** (12), and **3,4,6,7-tetramethyl-1*H*-azepine-2,5-dione** (14) were prepared by the procedure of Misiti, Moore, and Folkers;[16] **1*H*-benz[*f*]-azepine-2,5-dione** (16)[17] and **5*H*-morphanthridine-6,11-dione** (18)[19] were also prepared by literature methods. Physical constants and spectral properties of these diones were in agreement with those reported therein.

7-Ethoxy-2,5-dimethyl-4*H*-azepin-4-one (19).—A suspension of 10 (5.0 g, 0.033 mol) in dry CH_2Cl_2 was stirred with 6.3 g (0.033 mol) of $(C_2H_5)_3O^+BF_4^-$.[20] After 3 hr the starting material completely dissolved and the solution began to darken. At this point, the reaction was terminated by quenching with 50 ml of 10% aqueous K_2CO_3 solution. The organic layer was separated, dried (Na_2SO_4), and evaporated *in vacuo*. The residual tacky material was extracted with three 100-ml portions of pentane. Filtration and evaporation of the pentane left 255 mg of 19 (4.3%) which was purified by sublimation at ambient temperature at 0.1 mm. An analytical sample was prepared by dissolving 100 mg in 0.5 ml of CH_2Cl_2, depositing this solution on top of a 70 × 5 mm Woelm neutral, activity grade I, alumina column, and eluting with pentane. Evaporation of the pentane afforded pure 19: mp 57–58°; nmr (CCl_4) δ 6.70 (q, 1, vinyl H, J = 1 Hz), 6.13 (s, 1, vinyl H), 4.20 (q, 2, OCH_2CH_3, J = 7 Hz), 2.20 (s, 3, CH_3), 2.08 (q, 3, CH_3, J = 1 Hz), and 1.32 (t, 3, OCH_2CH_3, J = 7 Hz).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 66.99; H, 7.25; N, 7.81. Found: C, 67.03; H, 7.11; N, 7.88.

Hydrogenation of 23.—Hydrogenation of 150 mg (0.0010 mol) of 19 in 5 ml of 95% C_2H_5OH with 5% Pd/C at atmospheric pressure (2 hr) consumed 47 ml of hydrogen (0.002 mol). The solution was filtered and evaporated in a stream of dry nitrogen. Distillation of the residual oil at 42° (0.2 mm) gave 95 mg of **7-ethoxy-2,5-dimethyl-2,3,5,6-tetrahydro-4*H*-azepin-4-one** (20, 62%). The vpc and nmr data indicated the presence of two isomers: ir 1775 (C=O), 1590 (C=N), 1210, and 1040 cm^{-1} (=COC); nmr (CCl_4) δ 4.08 (doublet of q, 2, OCH_2CH_3, J = 7 Hz), 3.83–3.33 (m, 1, NCH), 3.08–1.91 (m, 5, ring protons), 1.32 (d, 3, CH_3, J = 6 Hz), 1.28 (d, 3, CH_3, J = 6 Hz), and 1.13 (t, 3, OCH_2CH_3, J = 7 Hz); vpc retention times 60 and 70 sec (6 ft × 1/8 in., 10% SE 30 column at 150°), 110 and 120 sec (6 ft × 1/8 in., 3% Apiezon L column at 125°). Carrier gas flow rate was 20 ml/min in both cases.

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.21; H, 8.45; N, 7.44.

Imino ether mixture 20 was also prepared by hydrogenation of 10 to the completely saturated isomer 21 followed by treatment with triethyloxonium fluoborate. Thus, hydrogenation (Parr shaker, 40 psi, 12 hr) of 10 (5.0 g, 0.033 mol) in 30 ml of 95% C_2H_5OH over 30% Pd/C (100 g) afforded, after catalyst removal and solvent evaporation, a viscous oil which solidified upon standing. Recrystallization from CH_2Cl_2–pentane followed by an ether wash gave 3.8 g (73%) of **4,7-dimethylhexahydro-1*H*-azepine-2,5-dione** (21): mp 166–168° (from CH_3CN); ir 3400, 3280 (NH), 1675 (C=O), 1680 and 1670 cm^{-1} (NCO); nmr (DMSO-d_6) δ 7.08 (mound, 1, NH), 4.62 (d, 2, =COH, J = 5 Hz), 4.00–1.42 (m, 5, ring protons plus enolic OH), 1.08 (d, 3, CH_3, J = 7 Hz), and 0.78 (d, 3, CH_3, J = 7 Hz); nmr (DMSO-d_6–D_2O) absorptions at δ 7.08, 4.62, and 4.00–1.42 (for one proton) disappear.

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.15. Found: C, 62.69; H, 7.55; N, 9.39.

A mixture of 21 (2.0 g, 0.013 mol) and 2.5 g of $(C_2H_5)_3O^+BF_4^-$ in 10 ml of CH_2Cl_2 was stirred overnight and quenched with 50 ml of 10% aqueous K_2CO_3 solution. The CH_2Cl_2 layer was separated, dried (Na_2SO_4), and evaporated *in vacuo* to give a

(33) Melting points and boiling points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 337 grating spectrophotometer utilizing potassium bromide wafers for solids and salt plates for liquids. The ultraviolet spectra were recorded on a Cary 15 dual-beam recording spectrophotometer using 95% ethanol as a solvent. The nmr spectra were obtained on a Varian Associates A-60A spectrometer with the solvent noted; chemical shifts are reported in parts per million (δ) downfield from TMS as the internal standard. Vpc analyses were performed on a Perkin-Elmer 880 gas chromatograph or a Perkin-Elmer F 21 preparative gas chromatograph. Microanalyses were determined by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. The mass spectra were obtained using the facilities of the Battelle Memorial Institute, High Resolution Mass Spectrometry Center, sponsored by the National Institutes of Health, Division of Research Resources, Contract No. NIH-69-2226.

light oil which was distilled [42° (0.2 mm)] to give the isomeric mixture **20** identical by all the usual criteria with **20** prepared from **19**.

5-Ethoxy-4,6,7-trimethyl-2*H*-azepin-2-one (22).—To a suspension of 5.0 g (0.03 mol) of **12** in anhydrous CH_2Cl_2 was added 6.0 g (0.032 mol) of $(C_2H_5)_3O^+BF_4^-$. The mixture was refluxed overnight, quenched by the addition of 10% aqueous K_2CO_3 solution (60 ml), and worked up in the manner described for isolation of crude **28**. The crystalline material isolated was dissolved in pentane, charcoaled (Darco), and filtered. The clear filtrate was concentrated, cooled, and filtered to give 3.4 g (63%) of **22** as colorless needles. An analytical sample was prepared by sublimation at 40° (0.1 mm): mp 71–72°; nmr (CCl_4) δ 6.68 (q, 1, vinyl H, J = 1 Hz), 4.25 (q, 2, OCH_2CH_3, J = 7 Hz), 2.30 (q, 3, CH_3, J = 0.5 Hz), 2.20 (d, 3, CH_3, J = 1 Hz), 2.08 (q, 3, CH_3, J = 0.5 Hz), and 1.37 (t, 3, OCH_2CH_3, J = 7 Hz).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.30; H, 7.76; N, 7.24; mol wt, 193.1103. Found: C, 68.53; H, 8.06; N, 7.24; mol wt, 193.1104 (mass spectrum).

5-Methoxy-4,6,7-trimethyl-2*H*-azepin-2-one (26, 51%) was prepared in a similar manner from **12** and $(CH_3)_3O^+BF_4^-$:[20] colorless; mp 52°; nmr (CCl_4) δ 6.68 (q, 1, vinyl H, J = 1 Hz), 3.77 (s, 3, OCH_3), 2.30 (q, 3, CH_3, J = 0.5 Hz), 2.20 (d, 2, CH_3, J = 1 Hz), and 2.10 (q, 3, CH_3, J = 0.5 Hz).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.22; H, 7.37; N, 8.08.

5-Ethoxy-3,4,6,7-tetramethyl-2*H*-azepin-2-one (28).—A suspension of 1.79 g (0.010 mol) of **14** in 15 ml of anhydrous CH_2Cl_2 and 1.90 g (0.010 mol) of $(C_2H_5)_3O^+BF_4^-$ was stirred overnight in a stoppered flask. Work-up was as follows. Aqueous K_2CO_3 solution (10%) was added slowly to the reaction mixture. The mixture was filtered to remove any inorganic material and the filter cake washed with CH_2Cl_2. The washings and filtrate were combined and the water layer was separated. Drying the organic layer (Na_2SO_4) and removal of the solvent *in vacuo* (no heat) led to a solid product. This material was extracted with pentane, the combined extracts were filtered, and the solvent was removed *in vacuo* to give **28** (1.44 g, 70%). Purification of **28** was achieved by dissolution in a small amount of CH_2Cl_2, deposition upon a 20 × 1 cm Woelm neutral alumina (activity grade I) column, and elution with pentane, giving 1.2 g of **28** as white needles. An analytical sample was sublimed at 40° (1.0 mm): mp 68.5–70°; nmr (CCl_4) δ 4.17 (q, 2, OCH_2CH_3, J = 7 Hz), 2.13 (q, 3, CH_3, J = 0.5 Hz), 2.10 (s, 6, CH_3), 1.97 (q, 3, CH_3, J = 0.5 Hz), and 1.10 (t, 3, OCH_2CH_3, J = 7 Hz).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27; N, 6.67; mol wt, 207.1259. Found: C, 69.39; H, 8.31; N, 6.60; mol wt, 207.1245 (mass spectrum).

5-Methoxy-3,4,6,7-Tetramethyl-2*H*-azepin-2-one (31, 63%) was prepared in a similar manner from **14** and $(CH_3)_3O^+BF_4^-$:[20] mp 84–85° (sublimation at 30°, 0.1 mm); nmr (CCl_4) δ 3.73 (s, 3, OCH_3), 2.13 (q, 3, CH_3, J = 0.5 Hz), 2.10 (s, 6, CH_3), and 1.97 (q, 3, CH_3, J = 0.5 Hz).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.64; H, 8.08; N, 7.53.

1,3,4,6,7-Pentamethyl-1*H*-azepine-2,5-dione (33).—To 50 ml of dry DMF was added 0.14 g(0.0058 mol) of pentane-washed sodium hydride. **14** (1 g, 0.0056 mol) and an excess of methyl iodide (1.15 g, 0.0080 mol) was then added and the solution was stirred at ambient temperature for 4 hr. The reaction mixture was poured into 200 ml of H_2O and the whole mixture was continuously extracted with hexane for 18 hr. The hexane was filtered to recover unreacted starting material. The filtrate was dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give 0.946 g (86%) of **33** as a yellow oil: bp 103° (1 mm); ir 1640 and 1635 cm^{-1} (C=O); uv max 241 nm (ϵ 13,000) and 330 (2300); nmr (CCl_4) δ 3.17 (s, 3, N=CH_3), and 2.07, 2.02, 1.95, 1.85 (all q, each 3, CH_3, J = 0.5 Hz).

Anal. Calcd for $C_{11}H_{15}NO_2$: N, 7.25. Found: N, 7.13.

Hydrogenation of 22.—An ethanolic solution of 1.93 g (0.010 mol) of **22** was hydrogenated (50 mg of 30% Pd/C) at atmospheric pressure and ambient temperature. The reaction stopped when 300 ml of hydrogen had been consumed (1.2 equiv); vpc analysis indicated all starting material had reacted. Filtration over Filter-Cel left a yellow solution containing a light oil. A vpc analysis indicated two minor products (*ca.* 10%) and one major product (*ca.* 90%). Initial distillation partially separated the mixture but prolonged heating decomposed the major compound. An analytical sample was obtained by preparative gc and redistilled to give **5-ethoxy-4,6,7-trimethyl-3,4-dihydro-1*H*-azepin-2-one (23)** as an oil which could not be induced to crystallize: bp 64° (0.1 mm); ir 1660 (C=O) and 1275 cm^{-1} (=COC); uv max 300 nm (ϵ 10,000); nmr (CCl_4) δ 4.20 (q, 2, OCH_2CH_3, J = 7 Hz), 1.68–2.22 (m, 3, CH and CH_2), 1.97 (q, 3, CH_3, J = 0.5 Hz), 1.82 (q, 3, CH_3, J = 0.5 Hz), 1.27 (t, 3, OCH_2CH_3, J = 7 Hz), and 1.10 (d, 3, CH_3, J = 7 Hz).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.76; N, 7.18. Found: C, 67.89; H, 8.61; N, 7.42.

4,6,7-Trimethyl-2,3,4,5-tetrahydro-1*H*-azepine-2,5-dione (24).—Partially purified **23** (1.0 g, 0.0050 mol) was dissolved in 5 ml of CH_2Cl_2 and deposited on a 20 × 1 cm alumina column (Woelm activity grade I, neutral). Successive elutions with pentane, carbon tetrachloride, methylene chloride, and chloroform afforded 250 mg (25%) of starting material. The column was stripped with methanol, and the solvent evaporated to give 640 mg (72%) of **24** as fine white needles, mp 94–96°. Two recrystallizations from hexane raised the mp to 101–102°: ir 1700, 1670, and 1665 cm^{-1} (C=O); uv max 295 nm (ϵ 10,900); nmr (CCl_4) δ 8.83 (mound 1, NH), 3.12–2.50 (m, 3, CH and CH_2), 2.12 (q, 3, CH_3, J = 0.5 Hz), 1.88 (q, 3, CH_3, J = 0.5 Hz), and 1.22 (d, 3, CH_3, J = 7 Hz).

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.68; H, 7.79; N, 8.38. Found: C, 64.43; H, 7.64; N, 8.15.

Tautomer **24** could be prepared directly from **12** in the following manner. A suspension of **12** (1.0 g, 0.0050 mol) in 95% C_2H_5OH was hydrogenated (5% Pd/C) at ambient temperature and atmospheric pressure. The reaction was terminated after slightly less than 1 equiv of hydrogen (150 ml) was taken up; after filtration of the catalyst, the solution was reduced in volume to 5 ml. A small amount of starting material precipitated from the chilled solution. Filtration and evaporation of the mother liquor left a residual oil. This oil was dissolved in a minimum amount of CH_2Cl_2 and deposited on a 20 × 1 cm Woelm, activity grade I, neutral alumina column and eluted with a 50:50 mixture of CH_2Cl_2–ether. Evaporation of the eluent afforded 720 mg (71%) of **24** as fine white needles, mp 100–101°, identical by all the usual criteria with **24** obtained from **23**.

Conversion of **24** to **23** was effected by treatment of the former (1.0 g, 0.0060 mol) in 50 ml of CH_2Cl_2 with $(C_2H_5)_3O^+BF_4^-$ for 18 hr. The solution was then washed with cold 10% aqueous K_2CO_3. The organic layer was separated, dried (Na_2SO_4), filtered, and evaporated. The residual colorless liquid was distilled at 69° (0.1 mm) to give 260 mg (23%) of **23** identical by all the usual criteria with **23** obtained by hydrogenation of **22**.

Hydrogenation of 26.—A solution of **26** (100 mg) in 10 ml of 95% C_2H_5OH was hydrogenated (10 mg 30% Pd/C) at room temperature and atmospheric pressure for 24 hr. Slightly more than 3 molar equiv of hydrogen (49 ml) was consumed. The catalyst was filtered and the filtrate evaporated *in vacuo* to give a clear oil, 68 mg (65%). Vpc analysis and nmr data confirmed the presence of four isomers: ir 3500, 3200, 1705, 1670, 1165, and 1095 cm^{-1}; nmr ($CDCl_3$) δ 3.98, 3.82 3.70, 3.63 (all s, 3, OCH_3), 3.33–1.67 (m, 6, ring protons + NH), 1.15 (d, 3, CH_3, J = 7 Hz), and 1.12 (d, 6, CH_3, J = 7 Hz); nmr ($CDCl_3$–D_2O) δ 3.33–1.67 (m, 5, ring protons) with no other alterations in the spectrum.

Hydrogenation of 28.—A solution of 250 mg (0.012 mol) of **28** in C_2H_5OH was hydrogenated (30% Pd/C) at atmospheric pressure. The reaction swiftly consumed 2 molar equiv of hydrogen (140 ml) and then ceased. The solution was filtered through Filter-Cel and the filtrate was evaporated in a stream of nitrogen with gentle warming. A white powder and a yellow oil were obtained. Washing with CCl_4 removed the oil and left 60 mg (22%) of crude **5-ethoxy-3,4,6,7-tetramethyl-1,3-dihydro-2*H*-azepin-2-one (32)**. This crude material was recrystallized from CH_2Cl_2–pentane only with substantial decomposition: mp 143–145°; ir 3400 (NH) and 1675 cm^{-1} (C=O); uv max 223 nm (ϵ 8800), 285 (5200), and 325 (4400); nmr ($CDCl_3$) δ 6.50 (mound, 1, NH), 3.27 (doublet of q, 2, OCH_2CH_3, J = 7 Hz), 2.67 (q, 1, CH, J = 7 Hz), 2.17, 1.90, 1.65 (all s, 3, =CCH_3), 1.23 (t, OCH_2CH_3, J = 7 Hz), and 1.16 (d, 3, CH_3, J = 7 Hz).

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69; mol wt, 209. Found: 68.52; H, 9.45; N, 6.37; mol wt, 209 (mass spectrum).

2,4-Dinitrophenylhydrazones.—The general procedure used was as follows.[34] To 100 mg (5.0 mmol) of 2,4-DNPH was

(34) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "Systematic Identification of Organic Compounds," 4th ed, Wiley, New York, N. Y., 1956, p 219.

added 0.5 ml of concentrated H_2SO_4 and 1 ml of H_2O. The mixture was then poured into 2.5 ml of 95% C_2H_5OH. An equimolar amount of the carbonyl compound in 5 ml of C_2H_5OH was added to the 2,4-DNPH solution. On standing overnight, the hydrazone precipitated; it was filtered, washed with cold C_2H_5OH, and recrystallized from ethyl acetate or C_2H_5OH.

Compounds **12**, **22**, and **26** gave the identical hydrazone **25**, mp 277–279°.

Anal. Calcd for $C_{15}H_{15}N_5O_5$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.00; H, 4.50; N, 20.42.

Similarly **14**, **28**, and **31** afforded the same hydrazone **30**, mp 215–217°.

Anal. Calcd for $C_{16}H_{17}N_5O_5$: C, 53.48; H, 4.77; N, 19.49. Found: C, 53.50; H, 4.80; N, 19.30.

2-Ethoxy-5*H*-benz[*f*]azepin-5-one (34).—To a solution of **16** (1.0 g, 0.0053 mol) in 50 ml of dry CH_2Cl_2 was added 1.1 g (0.0053 mol) of $(C_2H_5)_3O^+BF_4^-$ and the whole mixture was refluxed 3 hr. The green-black reaction mixture was quenched with 10 ml of 20% aqueous K_2CO_3 solution. The organic layer was separated, dried (Na_2SO_4), filtered, and evaporated to dryness. The green residue was sublimed [30° (0.1 mm)] to give **34** (70 mg, 6.5%). An analytical sample was obtained by chromatography on a 50 × 5 mm Woelm, neutral, alumina column (activity grade I). Elution with pentane gave **34** as white crystals: mp 46°; nmr (CCl_4) δ 8.08 (distorted d, 1, peri H, J = 8 Hz, 1.5 Hz), 7.58–7.10 (m, 3, aromatic), 6.81 (ν_B of AB quartet, 1, J = 12 Hz), 6.65 (ν_A of AB quartet, 1, J = 12 Hz), 4.31 (q, 2, OCH_2CH_3, J = 7 Hz), and 1.35 (t,3, OCH_2CH_3, J = 7 Hz).

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.92; H, 5.52. Found: C, 72.12; H, 5.82.

3,4-Dihydro-1*H*-benz[*f*]azepine-2,5-dione (35).—A suspension of 1.0 g (0.057 mol) of **16** in 25 ml of ethanol was hydrogenated overnight on a Parr shaker with 30% Pd/C at 40 psi. An additional 50 ml of C_2H_5OH was added and the whole mixture was filtered. The filtrate was concentrated *in vacuo* to give 0.87 g (86%) of **35**. Recrystallization from benzene led to a colorless product: mp 187–188°; ir 3250 cm^{-1} (NH); uv max 223 nm (ϵ 33,200), 254 (8800), and 317 (3300); nmr (DMSO-d_6) δ 8.00–6.70 (m, 5, aromatic + NH), and 3.08–2.50 (A_2B_2, 4, CH_2CH_2).

Anal. Calcd for $C_{10}H_9NO_2$: C, 68.50; H, 5.18; N, 8.01. Found: C, 68.64; H, 5.17; N, 8.31.

4-(*p*-Dimethylaminophenylimino)-3,4-dihydro-1*H*-benz[*f*]azepine-2,5-dione (36).—*N*,*N*-Dimethyl-*p*-nitrosoaniline (1.5 g, 0.010 mol) and **35** (1.0 g, 0.0060 mol) were dissolved in hot CH_3OH. A 2 *N* NaOH solution (2 ml) was added and on standing **36** precipitated as tiny red plates. The solid was filtered and repeatedly washed with acetone. Recrystallization from DMF gave 800 mg (50%) of **36** as red plates, mp 310–312°.

Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.20; H, 5.30; N, 13.82.

Concentrated HCl (10 ml) was added to 500 mg (0.0060 mol) of **36**. The mixture was heated (steam bath) for 30 min and the dark suspension was filtered on a sintered glass funnel. The residue was successively washed with H_2O, hot EtOH, and acetone to give 60 mg (11%) of **37**. This insoluble, yellow-green trione, mp 250° dec, defied all attempts at further purification: ir 3385 (NH), 1660, 1615, 1590, 1570 cm^{-1}.[35]

Anal. Calcd for $C_{10}H_7NO_3$: mol wt, 187. Found: mol wt, 187 (mass spectrum).

11-Ethoxybenz[*c*]cyclohexadienyl[5,6-*f*]-2*H*-azepin-2-one (42).—A suspension of **18** (10 g, 0.045 mol) in 200 ml of dry CH_2Cl_2 was treated overnight with 10 g (0.053 mol) of $(C_2H_5)_3O^+BF_4^-$. The previously described aqueous K_2CO_3 work-up afforded a white solid which was continuously extracted with pentane for 24 hr (Soxhlet). Evaporation of the pentane left a yellow solid which was dissolved in CH_2Cl_2, deposited on a 2 × 2 cm neutral, alumina column, and eluted with 30–60° petroleum ether to give **42** as white crystals (7.4 g, 71%). An analytical sample was prepared by recrystallization from pentane: mp 101–102°; nmr (CCl_4) δ 8.08–7.00 (m, 8 aromatic), 4.28 (q, 2, OCH_2CH_3, J = 7 Hz), and 1.44 (t, 3, OCH_2CH_3, J = 7 Hz).

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.45; H, 5.21; N, 5.61. Found: C, 76.29; H, 5.51; N, 5.65.

(35) To be compared with the carbonyl absorptions in **41**: 1660, 1620, 1590, and 1570 cm^{-1}.[30]

Compounds **18** and **42** gave the identical hydrazone **47**, mp 280° (from ethyl acetate).

Anal. Calcd for $C_{20}H_{13}N_5O_5$: C, 59.55; H, 3.25; N, 17.37. Found: C, 59.44; H, 3.29; N, 17.11.

11-Hydroxy-6(5*H*)-morphanthridinone (45).—A suspension of 10 g (0.045 mol) of **18** and 10 g (0.049 mol) of aluminum isopropoxide in 200 ml of dry isopropyl alcohol was slowly distilled through a 20-cm Vigreux column so that 1 drop of solvent was collected per minute. The distillate was tested for the presence of acetone by means of a 10% 2,4-DNPH solution. After two successive negative tests the reaction was assumed complete. Most of the isopropyl alcohol was removed *in vacuo* and the residue acidified with 100 ml of 10% HCl. The resulting solid was filtered, washed acid-free with water, and recrystallized from DMF–water to give 9.3 g (92%) of **45**: mp 247–248° (lit.[32] 250°); nmr (DMSO-d_6) δ 7.75–6.83 (m, 9, aromatic + NH), 6.12 (d, 1, OH, J = 5 Hz), and 5.62 (d, 1, CH, J = 5 Hz); nmr (DMSO-d_6–D_2O) δ 7.75–6.83 (m, 8, aromatic) and 5.62 (s, 1, CH).

11-Ethoxy-6-hydroxybenz[*c*]cyclohexadienyl[5,6-*f*]-2*H*-azepine (43).—A solution of 2.5 g (0.0010 mol) of **42** in 20 ml of wet THF was treated with a large excess of $NaBH_4$ (1.0 g, 0.030 mol). The mixture was stirred for 4 hr, poured into 100 ml of H_2O, and extracted with two 50-ml portions of ethyl ether. The ether layer was separated, dried (Na_2SO_4), and evaporated to give a viscous oil. Crystallization was induced by vigorous scratching. To effect recrystallization the solid was dissolved in CH_2Cl_2 and 30–60° petroleum ether was added to the cloud point. Upon standing at −10° crystals formed. This procedure was repeated to give a white solid: mp 105–106°; ir 3350 cm^{-1} (OH); uv max 210 nm (ϵ 36,800) and 285 (5700); nmr (CCl_4) δ 7.72–6.83 (m, 8, aromatic), 5.08 (s, 1, CH), 4.50 (m, 2, OCH_2CH_3) 3.29 (mound, 1, OH), and 1.47 (t, 3, OCH_2CH_3, J = 7 Hz).

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.04; H, 5.90; N, 5.79.

6-Hydroxy-5,6-dihydro-11-morphanthridinone (44).—A two-phase mixture of **43** (1.0 g, 0.0040 mol) and 20 ml of 1 *N* HCl was thoroughly stirred for 1 hr. The aqueous layer was separated and carefully adjusted to pH 6.9 by the addition of 1 *N* NaOH solution. The white precipitate that separated was filtered, washed with water, and recrystallized from C_2H_5OH to give dense white crystals: mp 138–139°; ir 3460 (OH), 3375 (NH), and 1740 cm^{-1} (C=O); uv max 215 nm (ϵ 42,500) and 295 (7500); nmr (CCl_4) δ 8.10–6.50 (m, 9, aromatic plus CH) and 3.82 (mound, 2, OH, NH, exchangeable with D_2O).

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.40; H, 4.86; N, 6.44.

11-Ethoxy-5-ethyl-6-morphanthridinone (46).—A suspension of **45** (2.25 g, 0.010 mol) in 15 ml of dry CH_2Cl_2 was treated with 1.90 g (0.010 mol) of $(C_2H_5)_3O^+BF_4^-$. After solution was effected, the reaction was quenched by the addition of 50 ml of 10% aqueous K_2CO_3. Methylene chloride (50 ml) was added to the mixture and the organic layer was separated, dried (Na_2SO_4), and evaporated *in vacuo* to leave a viscous oil. This oil was distilled at 120° (0.1 mm) to give 300 mg (11%) of **46** and a nondistillable glassy residue which could not be identified. The distillate solidified on cooling to −10° overnight. Recrystallization from CH_3OH gave white cubes: mp 67–68°; ir 1650 (C=O), 1145 and 1220 cm^{-1} (COC); uv max 230 nm (ϵ 21,600) and 280 (5000); nmr (CCl_4) δ 7.67–6.83 (m, 8, aromatic), 4.82 (s, 1, CH), 4.40 (doublet of q, 2, OCH_2CH_3, J = 7 Hz), 3.41 (mound, 2, NCH_2CH_3) (at 60°, q, 2, NCH_2CH_3, J = 6 Hz), 1.33 (t, 3, OCH_2CH_3, J = 7 Hz), and 1.15 (t, 3, NCH_2CH_3, J = 6 Hz).

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.82; N, 4.98. Found: C, 76.54; H, 6.65; N, 5.24.

Acid Hydrolysis of Azatropones.—The general procedure involved treatment of an alcoholic solution of the azatropone with a catalytic amount of H_2SO_4. After standing for several hours, a precipitate appeared. The mixture was cooled to −10°, filtered, washed with cold H_2O, dried, and recrystallized to quantitatively yield the corresponding azepinediones. Thus, **22** and **26** gave **12**, **28** and **31** led to **14**, and **42** afforded **18**.

Registry No.—**19**, 32516-06-6; **20**, cis, 32516-07-7; **20**, trans, 32513-34-1; **21**, cis, 32476-21-4; **21**, trans, 32513-55-6; **22**, 32476-22-5; **23**, 32513-35-2; **24**, 32513-36-3; **25**, 32513-37-4; **26**, 32513-38-5; **27**,

32513-39-6; **28**, 32513-40-9; **30**, 32513-41-0; **31**, 32513-48-7; **42**, 32513-49-8; **43**, 32513-50-1; **44**, 32513-42-1; **32**, 32513-43-2; **33**, 32513-44-3; **34**, 32513-51-2; **45**, 723-87-5; **46**, 32513-53-4; **47**, 32513-45-4; **35**, 16511-38-9; **36**, 32513-47-6; **37**, 54-5; tropone, 539-80-0.

Lithiation of Substituted Pyrazoles. Synthesis of Isomerically Pure 1,3-, 1,3,5-, and 1,5-Substituted Pyrazoles

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Four syntheses of isomerically pure substituted pyrazoles are described (A–D). Using a lithiation procedure, 1,3,5- and 1,5-substituted pyrazoles can be obtained directly, *e.g.*, (A) 1,3-dimethyl-α-phenylpyrazole-5-methanol (**5**) and 3-methyl-α-phenyl-1-propylpyrazole-5-methanol (**11**), (B) 5-methyl-α-phenylpyrazole-1-ethanol (**8**), and (C) α-phenyl-1-propylpyrazole-5-methanol (**16**). (A) Treatment of a 2:1 mixture of 1,3-dimethylpyrazole (**2**) and 1,5-dimethylpyrazole (**7**) with *n*-butyllithium equivalent to less than the amount of **2** followed by the addition of benzaldehyde yields **5**. (B) Lithiation of pure **7** and reaction with benzaldehyde yields **8**. (C) Reaction of 1-propylpyrazole (**15**) with an equivalent of *n*-butyllithium followed by the addition of benzaldehyde yields **16**. Pure 1,3-disubstituted pyrazoles were synthesized in high yield in two steps. 5-Chloro-1-methyl-3-substituted pyrazoles lithiate on the 1-methyl group. Thus (D) 5-chloro-1,3-dimethylpyrazole (**3**) was allowed to react with *n*-butyllithium followed by benzaldehyde yielding 5-chloro-3-methyl-α-phenylpyrazole-1-ethanol (**17**). Catalytic hydrogenation of **17** yielded 3-methyl-α-phenylpyrazole-1-ethanol (**6**). Two generalizations have been drawn concerning the position of metalation: (1) a 1-methyl substituent on a pyrazole will undergo metalation with *n*-butyllithium to some extent; (2) a pyrazole with an unactivated 1 substituent and a 5-H undergoes metalation exclusively on the 5 position. Changes in the nmr spectra in $CDCl_3$ and DMSO-d_6 have been useful in differentiating isomeric 1,3- and 1,5-disubstituted pyrazoles. A pyrazolyl ketone, 1,3-dimethylpyrazol-5-yl phenyl ketone (**25**), was synthesized by addition of an excess of benzaldehyde to the corresponding pyrazolyl lithium reagent.

Most syntheses of 1-alkylpyrazoles result in mixtures of 1,3- and 1,5-disubstituted pyrazoles. From these mixtures, pure products are obtained with difficulty if at all.[1-6] One of us had earlier found the synthetic utility of 5-chloro-1,3-disubstituted 4-lithiopyrazoles (available by halogen–metal exchange).[7,8] Thus we decided to investigate the lithiation of some readily available unsymmetrical pyrazoles, pyrazole isomeric mixtures, and the conversion of the resulting lithio reagents to isomerically pure substituted pyrazoles. A recent publication on the "Lithiation of Five-membered Heteroaromatic Compounds" including the lateral metalation of 1,3,5,-trimethylpyrazole (**1**)[9] has led us to report some of our results with unsymmetrical pyrazoles.

Habraken and Moore[6] have prepared pure 1,3-dimethylpyrazole (**2**) in 20% yield by Raney nickel catalyzed hydrogenation of 5-chloro-1,3-dimethylpyrazole (**3**). These workers also reported the positions of the nmr signals for the methyl substituents. A number of reports on the lithiation of 1-methylpyrazoles have appeared.[5,10] These workers isolated products corresponding to lithiation at the 5 position. Our reinvestigation of the lithiation of 1-methylpyrazoles has shown that lithiation also occurs on the 1-(lateral) methyl group. The earlier workers had relied upon the melting points of the acids resulting from the carbonation of the lithio intermediates, since most of the expected acids were known. Stock, Donahue, and Amstutz have reported that the combination of sodium ethoxide, diethyl oxalate, and 1-methylpyrazole (**4**) reacts on the 1-methyl group.[11]

We chose to react the lithio intermediates with benzaldehyde because of the higher yields, greater stability, lower water solubility, experimental ease, and nonamphoteric nature of the expected products. These products would most likely be unknown; however, it was felt that the nmr studies of Habraken and Moore,[6] Finar and Mooney,[12] as well as those of Tensmeyer and Ainsworth[13] and others,[14a-e] would allow differentiation between 1,3-, 1,5-, and laterally substituted pyrazoles. Vapor phase chromatography was performed on samples of the crude hydrolyzed reaction mixtures as well as on the final products to avoid missing noncrystalline products.

The reaction of pure 1,3-dimethylpyrazole (**2**) with an equivalent of *n*-butyllithium followed by benzaldehyde resulted in a 90% yield of a 2:1 mixture of 1,3-dimethyl-α-phenylpyrazole-5-methanol (**5**) and 3-methyl-α-phenylpyrazole-1-ethanol (**6**).

Because of the yield reported by Habraken and Moore[6] in their preparation of **2**, we also reinvestigated the reaction of 4,4-dimethoxy-2-butanone with methyl-

(1) L. C. Behr, R. Fusco, and C. H. Jarboe in "Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings," Interscience, New York, N. Y., 1967, pp 6–8 and 13–16.
(2) T. L. Jacobs in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1957, p 55.
(3) K. von Auwers and H. Hollmann, *Ber.*, **59**, 601, 1282 (1926).
(4) C. A. Rojahn, *ibid.*, **59**, 607 (1926).
(5) R. Hüttel and M. E. Schön, *Justus Liebigs Ann. Chem.*, **625**, 55 (1959).
(6) C. L. Habraken and J. A. Moore, *J. Org. Chem.*, **30**, 1892 (1965).
(7) H. A. DeWald and D. E. Butler, U. S. Patent 3,558,605 (Jan 1971).
(8) D. E. Butler and H. A. DeWald, *J. Org. Chem.*, **36**, 2542 (1971).
(9) R. G. Micetich, *Can. J. Chem.*, **48**, 2006 (1970).
(10) P. W. Alley and D. A. Shirley, *J. Amer. Chem. Soc.*, **80**, 6271 (1958).
(11) A. M. Stock, W. E. Donahue, and E. D. Amstutz, *J. Org. Chem.*, **23**, 1840 (1958).
(12) I. L. Finar and E. F. Mooney, *Spectrochim. Acta*, **20**, 1269 (1964).
(13) L. G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, **31**, 1878 (1966).
(14) (a) M. Cola and A. Perotti, *Gazz. Chim. Ital.*, **94**, 1268 (1964); (b) V. Papesch and R. M. Dodson, *J. Org. Chem.*, **30**, 199 (1965); (c) T. Yamanchi and J. A. Moore, *ibid.*, **31**, 42 (1966); (d) J. D. Albright and L. Goldman, *ibid.*, **31**, 273 (1966); (e) E. E. Zaev, V. K. Voronov, M. S. Shvartsberg, S. F. Vasilevsky, Yu. N. Molin, and I. L. Kotljarevsky, *Tetrahedron Lett.*, No. 5, 617 (1968).