pseudo-*p*-aminonitro[2.2]paracyclophane (**20**). A mixture of 70 mg of **20,** 4 ml of pyridine, and 4 ml of acetic anhydride was heated to 100° for 30 min, cooled, and mixed with 40 ml of water. The precipitate that formed was collected and recrystallized from ether to give 54 mg (77%) of needles of **38,** mp 227–228°. Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85. Found: C, 69.82; H, 5.94.

Similarly, pseudo-*m*-aminonitro[2.2]paracyclophane (**18**) was converted (88%) to pseudo-*m*-acetamidonitro[2.2]paracyclophane (**37**), mp 184–185° (C, 69.58; H, 5.85).

Acetamidoamino[2.2]paracyclophanes (39, 40). The pseudo-*p*-acetamidoamino[2.2]paracyclophane (**40**) was prepared from pseudo-*p*-acetamidonitro[2.2]paracyclophane (**38**). A mixture of 40 mg of **38,** 30 ml of ethyl acetate, and 50 mg of platinum oxide was stirred under an atmosphere of hydrogen until the hydrogen uptake stopped. The solution was filtered through Celite, the filtrate evaporated, and the remaining white solid was recrystallized from dichloromethane–pentane to give 29 mg (80%) of yellow needles of **40,** mp 245–247° dec. Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19. Found: C, 76.77; H, 7.26.

Similarly pseudo-*m*-acetamidonitro[2.2]paracyclophane (**37**) was converted (55%) to pseudo-*m*-acetamidoamino[2.2]paracyclophane (**39**), mp 223–224° dec (C, 77.05; H, 7.33).

Diamino[2.2]paracyclophanes (41, 42). Catalytic reduction in ethyl acetate with a platinum oxide catalyst of pseudo-*m*-aminonitro[2.2]paracyclophane (**18**) gave after sublimation and recrystallization from ethyl acetane–pentane–ether a 55% yield of pseudo-*m*-diamino[2.2]paracyclophane (**41**), mp 222–226° (sealed tube mp 239–244°). Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61. Found: C, 80.39; H, 7.36.

Similarly, pseudo-*p*-aminonitro[2.2]paracyclopane (**20**) gave (80%) pseudo-*p*-diamino[2.2]paracyclophane (**42**), mp 267–268° (sealed tube) (C, 80.67; H, 7.59).

Bromocarboxy[2.2]paracyclophanes (45, 46). A mixture of 317 mg of pseudo-*o*-bromocarbomethoxy[2.2]paracyclophane (**44**),[3b] 25 ml of 2 *N* sodium hydroxide, and 15 ml of absolute ethanol was refluxed for 5 days. The ethanol was evaporated and the basic aqueous solution was washed with chloroform and was acidified with hydrochloric acid. The precipitate that separated was collected and recrystallized from methanol to give 224 mg (68%) of pseudo-*o*-bromocarboxy[2.2]paracyclophane (**46**), mp 232–236°. Anal. Calcd for $C_{17}H_{15}BrO_2$: C, 61.65; H, 4.56. Found: C, 61.70; H, 4.62.

Similarly, pseudo-*m*-bromocarbomethoxy[2.2]paracyclophane (**43**)[3b] gave (82%), pseudo-*m*-bromocarboxy[2.2]paracyclophane (**45**), mp 218–219° (C, 61.88; H, 4.73).

Pseudo-*m*-carbomethoxynitro[2.2]paracyclophane (47). A solution of 88 mg of pseudo-*m*-carboxynitro[2.2]paracyclophane (**14**) in 20 ml of ether was treated with an excess of diazomethane in ether. The resulting solution was evaporated, and the residue was twice recrystallized from ether–pentane to give 60 mg (65%) of **47,** mp 130.5–132°. Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50. Found: C, 69.32; H, 5.50.

Pseudo-*m*-aminocarbomethoxy[2.2]paracyclophane (48). A mixture of 700 mg of pseudo-*m*-carbomethoxynitro[2.2]paracyclophane (**47**) was catalytically reduced with hydrogen and platinum oxide to give after recrystallization from ether 470 mg (74%) of **48,** mp 159–161°. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81. Found: C, 77.09; H, 6.83.

References and Notes

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.
(2) (a) This author thanks the Deutsche Forschungsgemeinschaft in Bad Godesberg, West Germany, for a Postdoctoral Fellowship; (b) Physikalisch-Chemisches Institut der Universität Basel.
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Meta Bridging Reactions of Electron-Deficient Aromatics. I. Studies Directed toward a One-Step Synthesis of the 6,7-Benzomorphan Ring System. Facile Preparation of Potential Narcotic Antagonists

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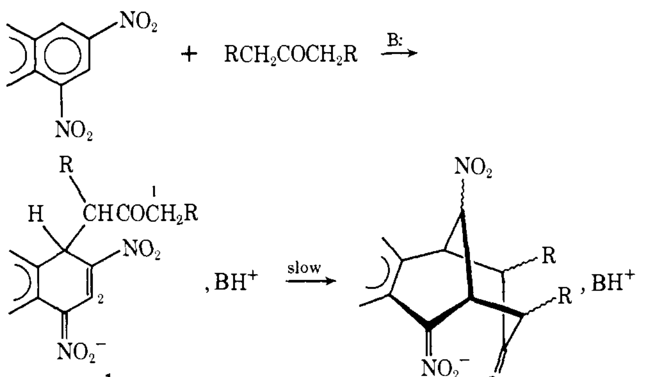
Abstract: Reactions of a series of amidines with electron-deficient benzenes and naphthalenes have been shown to yield addition products. In certain cases, cyclization of the initial adducts occurs to yield the 6,7-benzomorphan ring system. The reaction is a new and useful preparation of such structures which, when appropriately functionalized, may have useful narcotic analgesic and antagonist activity. The reactivity of the amidine σ complex precursors to the bridged products is of considerable interest, and new facets of the chemistry of nitrogen base σ complexes are discussed.

In a previous series of papers, we have extensively studied the reactions of potential biscarbanions with electron-deficient aromatics to yield carbobicyclic [3.3.1] ring systems.[1-8] The reactions are base catalyzed and occur in two distinct steps. The first intermediate to rapidly form is an addition adduct (σ complex) **1** which slowly cyclizes to the final product **2.**[7] Our attempts to employ such a sequence with types of potential biscarbanion precursors in which the two potential nucleophilic sites were not flanking a single carbonyl carbon always failed,[8] and a general consideration of the requirements of the cyclization process led us to conclude that an sp^2 center adjacent to the nucleophilic site in



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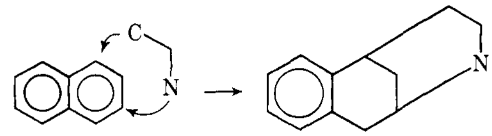
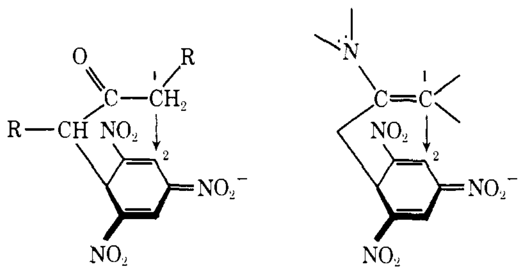


a 6,7-benzomorphan

the side chain and β to the ring in the initial intermediate addition complex is necessary for the cyclization to occur. Such a geometry brings C_1 and C_2 in structures like **1** or **3** into close proximity and facilitates ring closure. A similar geometry in the enamine addition adduct of *sym*-trinitrobenzene (TNB) (**4**) also provides for a close interaction of



3 4

the enamine carbon C_1 and the electrophilic ring carbon C_2, and this intermediate also readily cyclizes to the carbocyclic [3.3.1] system containing an exocyclic nitrogen function (immonium ion).[2] We hoped that any intermediate addition complex containing the appropriate geometrical relationships between the reactive nucleophilic and electrophilic sites would be capable of cyclizing to the [3.3.1] ring structure. Substitution of heteroatoms for carbon could then provide a useful new way to synthesize bicyclic structures which previously required much longer and more expensive routes. This paper is the first in a series which will deal with new methods of preparing such heterobicyclic ring systems and is concerned with mechanistic and product studies of reactions leading to compounds having the basic 6,7-benzomorphan skeleton.

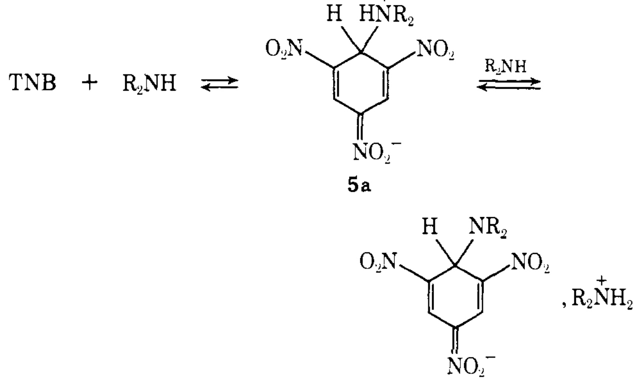
For over a decade, intense interest in analgesic benzomorphans has been prompted by observations of some dissociation of analgesia and dependence. The syntheses of hundreds of benzomorphans have been carried out in numerous laboratories.[9-14] In most instances, these syntheses involve many steps. A recent synthesis of the parent 6,7-ring system, which is pharmacologically active, has been reported by May.[14] It involves ten steps starting from 4-phenylpyridine. Interestingly, other recent research has shown that the quaternary carbon and phenolic hydroxyl usually thought vital for physiological activity are in fact not necessary.[10,13,14] A simple and economical *one-step* synthesis of such compounds could thus be quite valuable.

It became obvious to us that meta bridging could provide the 6,7-benzomorphan ring structure in a single step if an electron-deficient naphthalene were bridged by a potential bisnucleophile containing appropriately positioned nucleophilic carbon and nitrogen. The work described here outlines our efforts to achieve such a one-step bridging reaction and summarizes structural features of the substrates which are necessary for such bridging to readily occur. The chemistry of anionic σ complex intermediates involved illustrates some interesting new aspects of organic nitrogen and carbon base reactivity toward electron-deficient aromatics, a subject which has generated considerable interest during the past decade.[15-17]

Reactions of Amidines with TNB

A potentially effective meta bridging function can be envisioned in the amidines. Primary and secondary amines react readily with TNB to yield σ complexes according to the sequence shown in Scheme I.[15e,16,17] If R in the depicted reaction has an appropriately positioned potential nucleophilic site, then further reaction might easily occur to yield a meta bridged product. Amidines provide the appropriate functionality, and the reactions we have observed with TNB and several acetamidines are summarized in Scheme II.

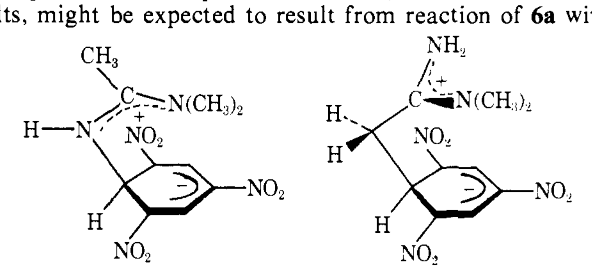
Scheme I



5a 5b

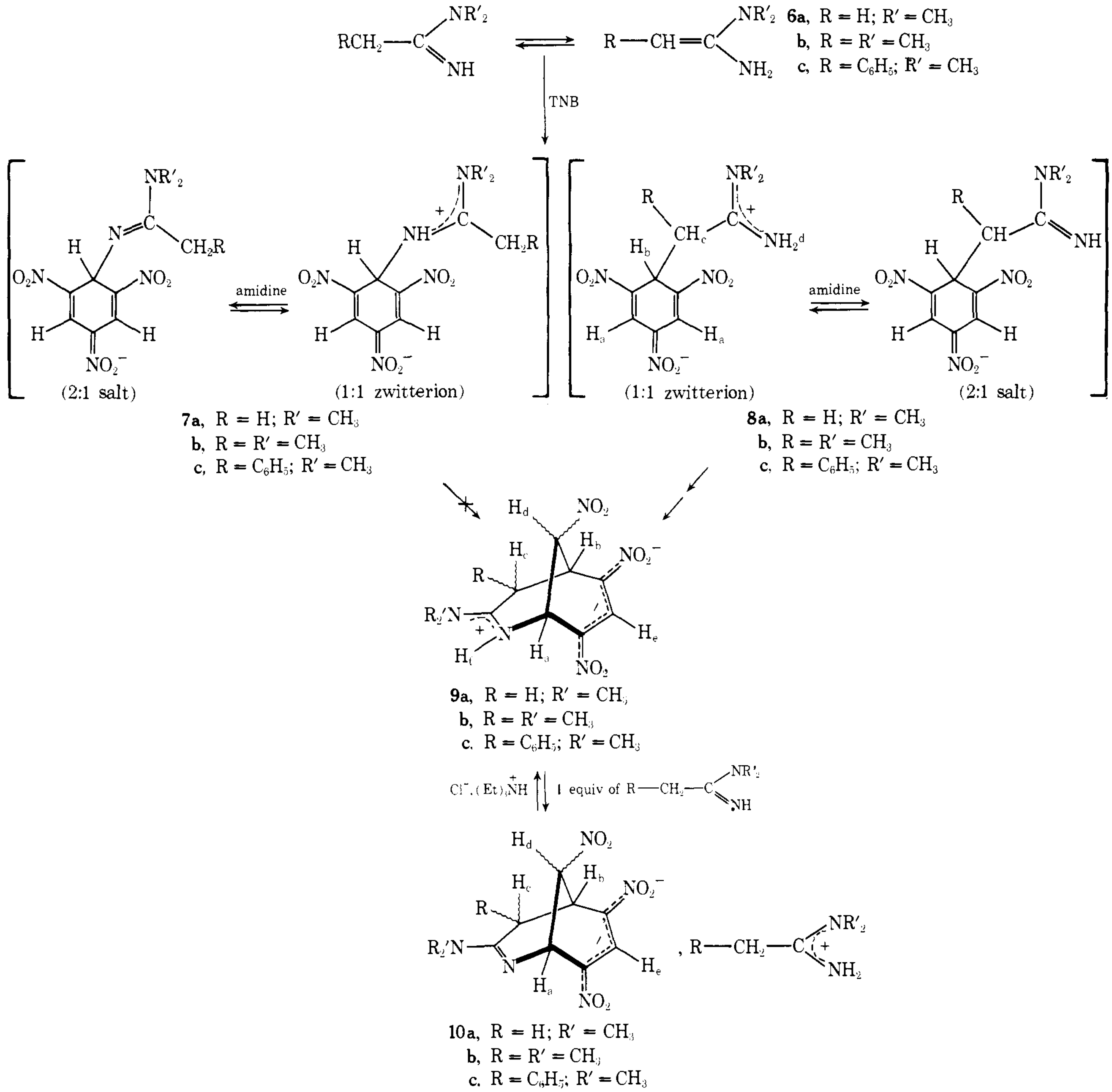
N,N-Dimethylacetamidine (**6a**) was generated in situ in ethanol solution by adding 1 equiv of hydrochloride salt to 1 equiv of an ethanolic solution of sodium. One equivalent of TNB in ethanol was added to the amidine solution. Alternately the amidine could be distilled from the initial ethanol solution, and the reaction with TNB could be run in DMSO solution or ethanol solution. The mixtures immediately turned very dark orange with visible maxima characteristic of anionic σ complexes.[15] Work-up of the ethanolic mixture (see Experimental Section) provided an 81% yield of a crystalline σ complex as the sole product which analyzed correctly for a 1:1 adduct of amidine and TNB. The visible spectrum of this product in DMSO showed two maxima at 460 and 567 nm. Running the reaction in excess amidine provided high yields of the *same* σ complex product. There was no evidence for conversion to a 2:1 σ complex adduct (salt) or cyclized product (**9a**).

A priori both complexes **7a** and **8a**, as their amidinium salts, might be expected to result from reaction of **6a** with



7a 8a

Scheme II



TNB, analogous to the formation of **5b** from the reaction of TNB with primary or secondary amines.[15e,16,17,18b] The analysis indicating a 1:1 equivalent ratio of aromatic and amidine must mean that the reaction has terminated at the zwitterionic form of either **7a** or **8a** analogous to **5a.** Since zwitterionic complexes like **5a** *have never before been isolated as stable products,*[16,17] there must be some significant structural difference between amine and amidine zwitterionic complexes which contributes to the stability of the latter. In considering the structures of **7a** and **8a,** it should be noted that they differ considerably from each other in geometrical distribution of charge. The delocalized π systems of the cationic and anionic moieties in the zwitterionic form of **7a** are orthogonal whereas in **8a** they are more properly aligned for a stabilizing π overlap interaction. If complex stability is more important than a kinetic preference for attack by the most stable tautomer of the amidine (i.e., C═N rather than C═C), then complex **8a** would be the expected product.

It is interesting to note that Bernasconi has reported the visible spectrum of the unstable zwitterionic complex **5a** (HN^+R_2 = piperidinium) obtained by an indirect method[16,17] and has compared it with the spectrum of the stable anionic counterpart **5b.** The latter has maxima at ~445 and ~520 nm, whereas the former has maxima at ~460 and ~560 nm, and Bernasconi has commented on this bathochromic shift on going from the anionic to zwitterionic complex. He has pointed out the possibility of intramolecular hydrogen bonding with an ortho nitro group in **5a** which could affect the absorption maxima. This rationalization was based on comparisons with visible spectra of previously reported tertiary amine zwitterionic complexes[19,20] which supposedly could not have such hydrogen bonding. Since these tertiary amine zwitterions have since been shown to be anionic,[18] a hydrogen bonding rationalization of the bathochromic shift seems less viable. In fact, compilations of σ complex spectra in earlier reviews[15] show that visible maxima of trinitrocyclohexadienate complexes appear to be very dependent on the electronegativity of the atom bonded to the tetrahedral carbon of the ring. The visible maxima of the complex we have isolated are characteristic of trinitrocyclohexadienate complexes formed with carbon bases,[15]

Table I. ^{1}H NMR Spectral Data for the Isolated Nitroaromatic Addition Adducts (DMSO-d_6, Parts per Million, δ, Relative to Internal Me_4Si Except Where Noted[d]

Compd	H_a	H_b	H_c	H_d	H_e	H_f	H_g	R	NCH_3	Other protons	Cation
8a	8.15 (s, 2 H)	5.04 (t, 1 H) J_{bc} = 6	2.61 (d, 2 H) J_{bc} = 6	8.15 (br, 1 H)[b] 8.63 (br, 1 H)[a]				See H_c	2.91 (s, 3 H)[b] 3.35 (s, 3 H)[a]		
8b	8.43 (d, 1 H)[c] 8.51 (d, 1 H)[c] J'_{aa} = 1.5	5.27 (d, 1 H) J_{bc} = 3.5	3.5 (m, 1 H)[c]	8.25 (br, 2 H)				1.04 (d, 3 H) $J_{R,c}$ = 7.0	3.02 (s, 3 H)[b] 3.48 (s, 3 H)[a]		
9c	5.34 (dd, 1 H)	4.15 (br, 1 H)	4.76 (br, 1 H)	5.92 (d, 1 H)	8.29 (s, 1 H)	10.15 (br, 1 H)		7.40 (m, 5 H)	2.96 (s, 6 H)		
10c	4.01 (br, 1 H) 4.16[e]	4.58 (dd, 1 H) 4.54[e]	3.76 (1 H)[f] 3.97[e]	5.45 (m, 1 H) 5.71[e]	7.86 (s, 1 H) 8.19[e]			7.04 (m, 5 H)[f] 7.11[e]	2.47 (s, 4 H) (s, 6 H) 2.56[e]		C_6H_5, 7.04 (m, 5 H); 3.97[e] CH_2, 3.86 (s, 2 H); 3.88[e] NH_2, 8.60 (br, 2 H); 7.99[e] CH_3, 2.97 (s, 6 H); 3.06[e]
19d	5.35 (dd, 1 H)	4.25 (br, 1 H)	5.01 (br, 1 H)	6.29 (dd, 1 H)	8.56 (d, 1 H) J_{eg} = 2	10.31 (br, 1 H)	8.25 (d, 1 H) J_{eg} = 2	7.42 (brs, 5 H)	2.89 (br s, 6 H)		
21d	4.91 (dd, 1 H)	4.44 (brs, 1 H)	3.94 (1 H)[f]	6.19 (dd, 1 H)	8.49 (d, 1 H) J_{eg} = 2		8.25 (d, 1 H) J_{eg} = 2	7.36 (m, 5 H)[f]	2.97 (s, 6 H)		C_6H_5, 7.36 (m, 5 H) CH_2, 3.98 (s, 2 H) NH_2, 8.11 (br, 1 H) 8.72 (br, 1 H) CH_3, 3.08 (s, 6 H)
21b[l]	4.58 (1 H)[k]	4.04 (1 H)[f]	4.58 (1 H)[k]	6.03 (br m, 1 H)	7[h]		7[h]	7.22 (m, 5 H)[f]	2.50 (s, 6 H)	R' = H (between H_e and H_g at 7[h] peri R' = H at 8.88 (d, 1 H)[i] J = 9	C_6H_5, 7.22 (m, 5 H) CH_2, 4.04 (s, 2 H) NH_2, 9.50 (br, 2 H) H_3, 3.03 (s, 6 H)
17c	8.22 (s)[g]	4.90 (t, 1 H) J_{bc} = 6	2.73 (m, 2 H)[c]	8.09 (br, 1 H)[b] 8.65 (br, 1 H)[a]	8.22 (br)[g]		8.37 (br)	See H_c	3.29 (s, 3 H)[a] 2.95 (s, 3 H)[b]		
17a[j]	8.69 (s, 1 H)	4.74 (t, 1 H) J_{bc} = 7	2.70 (d, 2 H) J_{bc} = 7	8.50 (br, 2 H)	7.16[h]		7.16[h]	See H_c	3.12 (s, 6 H)	R' = H (between H_e and H_g at 7.16[h] peri R' = H at 8.60 (d, 1 H)[i] J = 9	

[a] Inside. [b] Outside. [c] Nonequivalent due to asymmetric center α to or on the tetrahedral ring carbon (see M. I. Forman, R. Foster, and M. J. Strauss, *J. Chem. Soc.*, **12**, 147 (1970). [d] 100 MHz. [e] In $CDCl_3$. [f] Overlaps cation absorption. [g] H_e and H_a absorptions overlap to give a broad 2 H peak. [h] Overlaps with other absorptions on the unsubstituted aromatic ring. [i] R' = H peri to nitronate functionality. [j] Contains 1 equiv of DMSO of crystallization with absorption at δ 2.52 (s, 6 H) confirmed by elemental analysis (see Table II). [k] H_a and H_c overlap. [l] Contains 1 equiv of ethanol of crystallization with absorption at δ 1.04 (3 H, t) and 3.80 (2 H, q) confirmed by elemental analysis (see Table II).

Table II. Elemental Analyses of Isolated Nitroaromatic Addition Adducts

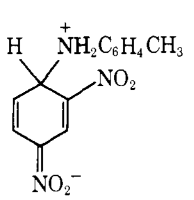
Compd	C Found Calcd	H Found Calcd	N Found Calcd
8a	40.31	4.62	23.35
	40.14	4.38	23.40
8b	42.20	5.13	22.15
	42.17	4.83	22.36
9c	51.15	4.63	18.45
	51.20	4.57	18.66
10c	57.86	6.04	18.03
	58.09	5.81	18.24
19d	51.34	4.01	17.45
	51.07	3.86	17.87
21d	57.18	5.32	17.41
	56.96	5.10	17.71
19b[c]	62.17	5.72	14.06
	62.11	5.59	14.13
21b[a]	65.30	6.50	14.84
	65.82	6.59	14.86
17c	42.93	3.69	19.07
	42.65	3.58	21.31
17a[b]	57.86	6.04	18.03
	58.09	5.81	18.24

[a] Contains 0.5 equiv of CH_3CH_2OH of crystallization. [b] Contains 1 equiv of DMSO of crystallization. [c] Contains 0.5 equiv of CH_3OH of crystallization.

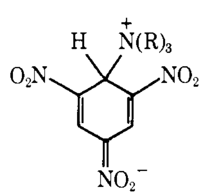
which provides evidence for **8a.** The ^1H NMR spectrum in DMSO-d_6 confirms its zwitterionic character and fully supports carbon attack yielding structure **8a** (see Table I).

Substitution of an α-methyl group on **6a** provides *N,N*-dimethylpropionamidine (**6b**) which reacts with TNB to yield the analogous zwitterionic σ complex **8b.** This complex has spectral properties quite similar to those of **8a** and is not converted to its salt in the presence of excess amidine. In addition, there was no evidence for cyclization to **9b.** The complex was characterized by ir, ^1H NMR, and elemental analysis (see Tables I and II and the Experimental Section).

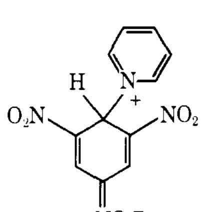
The stability of **8a** and **8b,** both of which can be isolated as crystalline solids, is remarkable. This is especially so since earlier proposals for the stable zwitterionic complexes **11–14** have all been shown incorrect.



11



12a, (R = CH_3)
b, (R = CH_2CH_3)



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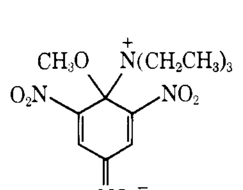

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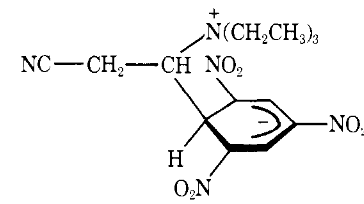
In the case of **11–13,** the proposals[19-24] were made because solutions of the reactants exhibited double maxima in the visible region characteristic of anionic σ complexes.[15] A definitive study by Crampton and Gold[18b] has shown that these absorptions undoubtedly arise from secondary amine impurities leading to **5b,** and that carefully purified tertiary amine does not react or yield colored solutions with TNB.[18b] The ^1H NMR spectrum originally attributed to **14** has subsequently been shown to arise from methyltriethylammonium picrate.[25] The only zwitterionic σ complex previously isolated as an analytically pure solid is **15,** and



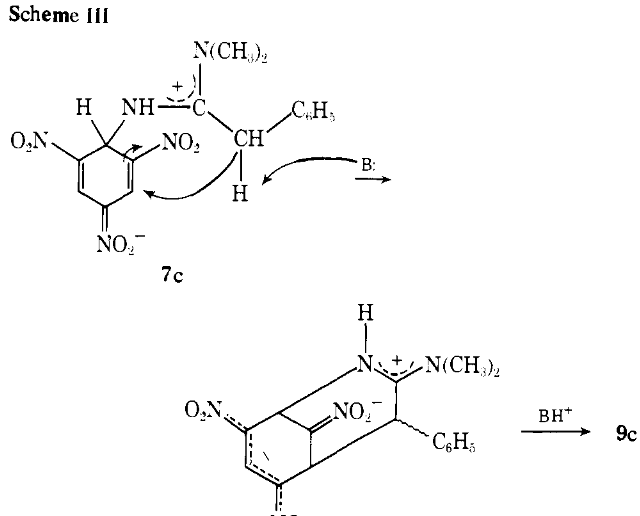
15

since it rapidly decomposes in DMSO, the only solvent in which it is soluble, a thorough ^1H NMR characterization of structure is impossible.[25] It is interesting to note that the positive charge in **15** is one carbon removed from the anionic ring, perhaps allowing for an attractive stabilization similar to that which we have proposed here for **8a** and **8b.**

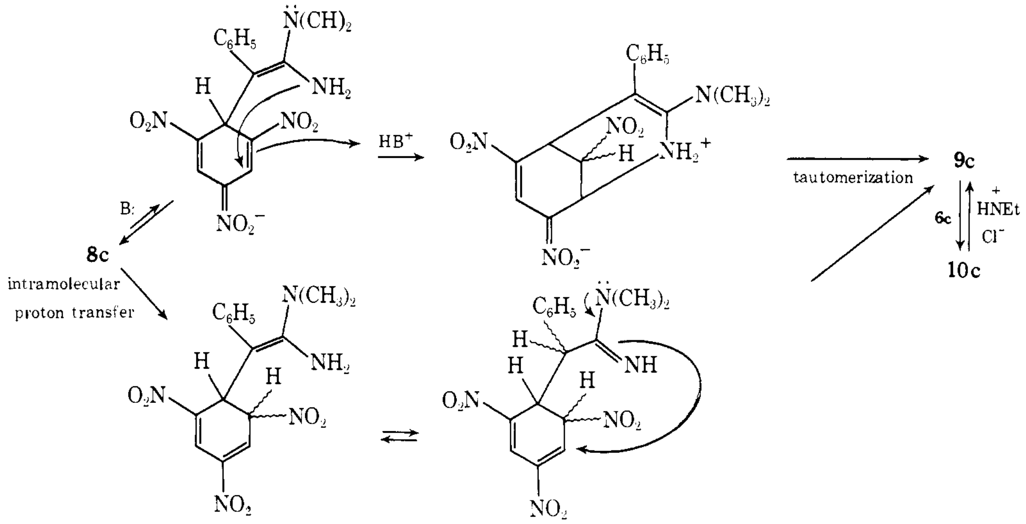
Substitution of an α-phenyl group on **6a** causes a profound difference in reactivity of the resulting α-phenyl-*N,N*-dimethylacetamidine **6c** compared with both **6a** and **6b.** In very dilute solutions of amidine and TNB ($\sim 10^{-4}$ *M*) in DMSO, visible maxima characteristic of anionic σ complex intermediates rapidly appear and then disappear as a strong maximum at ~500 nm develops, characteristic of the nitropropene nitronate function in **9** or **10.**[5] Attempts to observe σ complex intermediates by examining the ^1H NMR spectrum of a more concentrated solution of reactants failed as the higher concentrations necessary for ^1H NMR analysis resulted in almost instantaneous conversion to the final product. Reaction of 1 equiv of **6c** with 1 equiv of TNB in either ethanol or DMSO yields a 1:1 adduct of amidine and aromatic with ^1H NMR, visible, ir, and elemental analysis consistent with **9c.** The ^1H NMR spectrum is especially definitive when it is compared with that of carbocyclic analogues of such systems prepared previously[1-8] (see Experimental Section).

It is interesting to speculate on why substituting C_6H_5 for CH_3 on going from **6b** to **6c** should facilitate cyclization in complexes of the latter. Since the initial σ complex intermediate(s) cannot be observed, cyclization could be presumed to occur through *either* **7c** or **8c.** It could be that C_6H_5 functionality precludes formation of **8c** merely because of its bulk and the resulting added hindrance to nucleophilic carbon attack. If this were so, **7c** could readily cyclize by the same mechanism previously confirmed for formation of the carbocyclic dibenzyl ketone adduct of TNB[7] (Scheme III). Since the anion of dibenzyl ketone readily attacks

Scheme III



Scheme IV



TNB,[7] this explanation seems most unlikely since this anion is at least as hindered (perhaps more so) than the amidine **6c**. It is much more likely that **8c** is the direct precursor to **9c**, and the facile cyclization results from increased acidity of the remaining α proton of the amidine moiety in **8c** relative to **8a** and **8b**. It is obvious, based on previous mechanistic studies of related carbanionic cyclizations of this kind,[7,8] that **8c** cannot cyclize in its zwitterionic form since the exocyclic cationic side chain is certainly not nucleophilic. It must first be converted to a neutral or anionic form by reaction with another mole of amidine or by intramolecular proton transfer to the anionic ring. The reaction with more amidine would be an equilibrium, the position of which would be determined by the relative pK_b's of free amidine and amidine functionality in the complex. Since the zwitterionic amidinium form of **8a** and **8b** cannot be converted to the anionic form by free amidine (vide supra), it appears that this equilibrium would lie far tc the left for **8a, 8b,** and **8c.** The α-phenyl substitution in **8c** would result in an increase in the acidity of the remaining α proton relative to the α proton in α-methyl substituted or unsubstituted acetamidine complexes **8b** and **8a.** This would provide a pathway for base- catalyzed cyclization of **8c** which is less likely for **8a** or **8b.** The cyclization could be base catalyzed by amidine or proceed by an initial intramolecular proton transfer (Scheme IV).

Interestingly, addition of 2 equiv of **6c** to TNB or addition of 1 equiv to the bicyclic zwitterion **9c** yields the bicyclic compound **10c,** which can be isolated as a crystalline salt and characterized by ^{1}H NMR, ir, and visible spectroscopy as well as elemental analysis. It appears that the equilibrium between the bicyclic adducts **9c** and **10c** lies far toward the latter in the presence of excess amidine, in contrast to the open chain forms of **8a** and **8b.** This is not unexpected considering the unusual stability of the zwitterionic forms of **8a** and **8b** noted above. In the presence of the relatively strong acid triethylammonium chloride, **10c** is quantitatively converted back to the zwitterionic form **9c.**

There appear to be no other side reactions leading to products other than **8** and **9** in the reaction of TNB with the amidines studied. Such is not the case with TNN, however, where complicating side reactions may appear depending on amidine concentration and solvent (ethanol or DMSO).

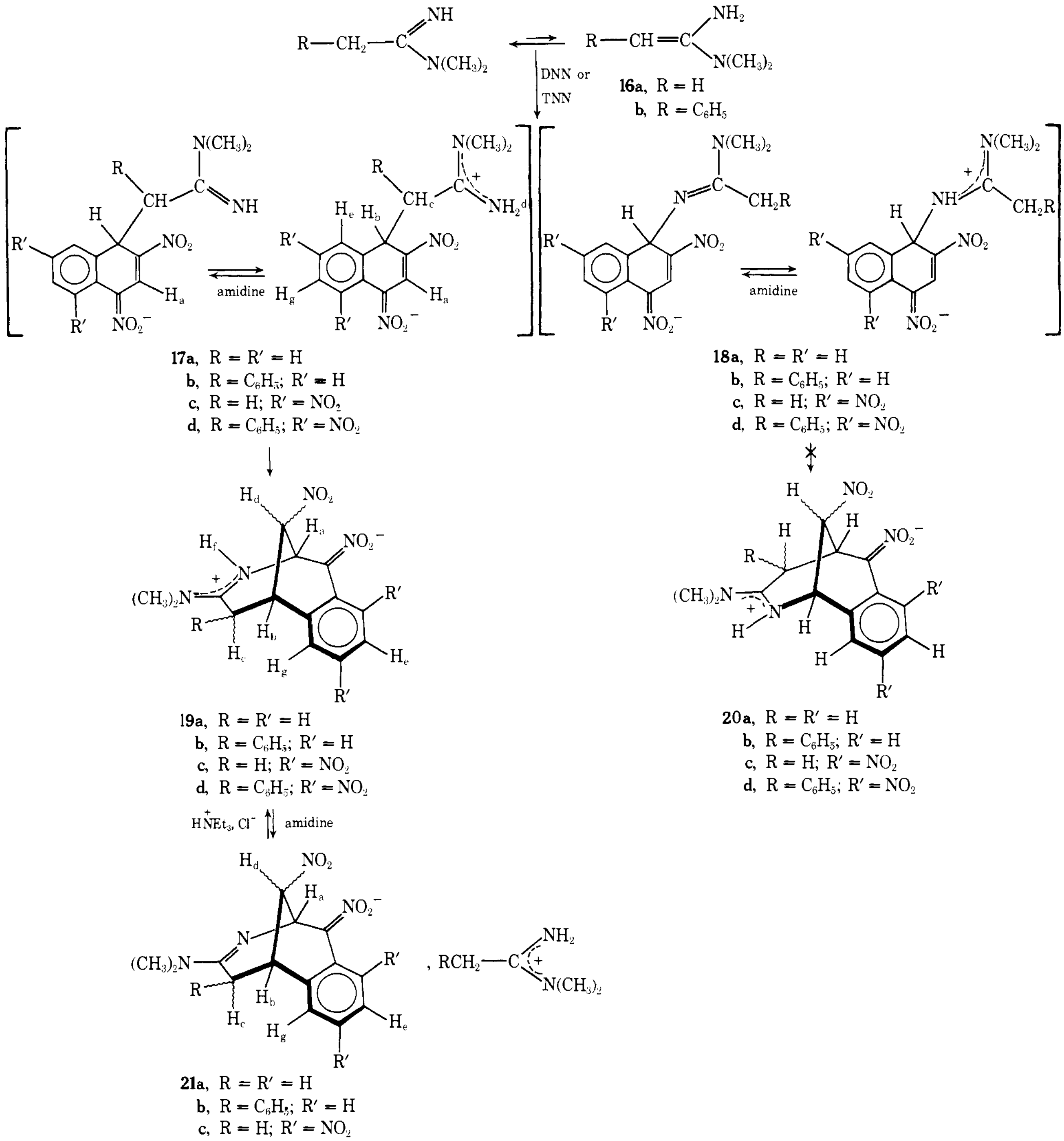
Reactions of electron-deficient naphthalenes with amidines are quite similar to those of TNB, with the added complication of possible isomeric bridged adducts. The general sequence of reactions observed is outlined in Scheme V.

Analogous to the reaction with TNB, *N,N*-dimethylacetamidine (**16a**) reacts with TNN in DMSO to yield the isolable crystalline σ complex **17c** *in its zwitterionic form* as the sole product. This structure has been characterized by ^{1}H NMR, ir, and elemental analysis. Reaction of 1,3-dinitronaphthalene (DNN) with **16a** yields the analogous product **17a.** It is clearly established from the ^{1}H NMR spectra of these zwitterionic complexes that *carbon* and not nitrogen of the amidine becomes bonded to C-1 in the complex. *There is no evidence at all for* **18a** *or* **18c** *in the reactions of DNN and TNN.*

Two important points are now clearly established from observations of the reactions of TNB, DNN, and TNN with amidines which lead to σ complex addition adducts. Firstly, *initial carbon attack on the aromatic occurs rather than nitrogen attack.* This type of behavior is commonly observed in nucleophilic reactions of amidines. In addition, in naphthalenes, this attack occurs at an *α position opposite a para nitro group,* rather than at a β position between two nitro groups. It could be that β attack occurs very rapidly, followed by rapid isomerization to the product of α attack. If this does occur, it is much too rapid to be detected by ^{1}H NMR of the reaction solutions. It should be noted that similar $\beta \rightarrow \alpha$ isomerizations have been proposed for oxygen base systems in their reactions with electron-deficient naphthalenes.[5] These were detected by stopped flow visible spectroscopic methods, however. In such experiments, the concentrations of reactants are several orders of magnitude different from those used in our preparative and ^{1}H NMR studies.

Considering the above observations and also the results obtained in reactions of TNB with various amidines, we concluded that α-phenyl-*N,N*-dimethylacetamidine (**16b**) would react with TNN and DNN to yield meta bridged products containing the 6,7-benzomorphan ring structure. It might be considered possible that the product from initial *α nitrogen* attack on DNN or TNN, **18b** or **18d,** is initially formed and could rapidly cyclize to **20b.** The experiments with TNB do not preclude such a possibility since the cyclized product in this case would be the same (i.e., **9**) regardless of the intermediate σ complex precursor which cannot be characterized. The final products resulting from reaction of **16b** with TNN and DNN can be isolated and characterized, however, and such characterization confirms structures **21b** and **21d** (vide infra). These products are obtained by treating 1 equiv of the aromatic with 2 equiv of **16b** (see Experimental Section). They are readily converted to the zwitterionic forms, **19b** and **19d,** by treatment with triethylammonium chloride. The bicyclic zwitterions cannot

Scheme V



be prepared by reaction of 1 equiv of aromatic and 1 equiv of amidine as with TNB. A mixture of inseparable σ complex and bicyclic addition adducts is obtained under these conditions.

¹H NMR Spectra of the Isolated Addition Adducts

The ¹H NMR spectral data for the various addition products are summarized in Table I. Several interesting trends are apparent when comparisons of chemical-shift values for the zwitterionic and anionic adducts are made. For example, in considering the four protons on the bicyclic portion of the zwitterionic and anionic bicyclic adducts of TNN and α-phenyl-*N*,*N*-dimethylacetamidine (H_a, H_b, H_c, and H_d in **19d** and **21d**), it is important to note that the greatest change in shift in going from zwitterion **19d** to anion **21d** occurs with those protons adjacent to the amidinium-amidine functionality. Upfield changes in shift values ($\Delta\delta$) of 0.44 and 1.07 ppm occur for H_a and H_c, respectively, whereas H_d and H_b both shift less than 0.2 ppm upfield on going from **19d** to **21d.** Such behavior would be predicted based on a simple electronegative deshielding of the protons adjacent to amidinium functionality in **19d** which is absent in **21d.** Such effects are even smaller further from the functionality which is changing. The aromatic ring protons in going from **19d** to **21d** shift less than 0.1 ppm. Effects similar to these are observed in the zwitterionic and anionic adducts with TNB where the upfield shifts of H_a and H_c in going from **9c** to **10c** are both over 1.0 ppm. The anomalous downfield shift of H_b on going from zwitterion **9c** to anion **10c** could be due to a conformational change of the adjacent phenyl group which puts H_b in a deshielding region of this moiety. A larger series of related compounds must be examined before a more definitive understanding of these values can be made.

It is quite interesting to note that the nitropropene nitronate proton H_e in **9c** and **10c** shifts 0.43 ppm upfield on going from the former to the latter. This shift is probably indicative of significant interaction of the amidinium functionality in zwitterion **9c** with the nitronate functionality across the ring which could stabilize **9c.** It is clear from models of these compounds that the distance between these functionalities is too great for a direct orbital overlap stabilization. Hydrogen bonding of one nitronate oxygen to amidinium hydrogen in **9c** but not **10c** could well result in such an effect.

Unfortunately the zwitterionic bicyclic complex of DNN and α-phenyl-*N,N*-dimethylacetamidine (**9b**) is so insoluble that its ^{1}H NMR spectrum could not be measured in any solvent, and comparison with the spectrum of the anionic complex **21b** could not be made. Heating solutions of **19b** in DMSO resulted in quantitative disproportionation to **21b** and DNN.

Discussion of Elemental Analyses

We experienced considerable difficulty in obtaining satisfactory elemental analyses for the isolated addition adducts. These highly polar molecules have very strong tendencies to crystallize with occluded solvent. In addition, the rather large nitrogen content caused some difficulty, because certain analytical laboratories did not have proper standardization procedures for nitrogen in the 20% range. After correcting this problem and after drying the finely ground crystals with a mercury diffusion pump for 12 hr at elevated temperatures, analytically pure samples were obtained in all cases except for the adducts **21b** and **17c.** The analytical results were double checked by two different laboratories: G. I. Robertson Laboratories, Florham Park, N.J., and Galbraith Laboratories, Knoxville, Tenn. Of the ten compounds analyzed, only **17c** gave a low value for nitrogen, and **21b** gave a low value for carbon. The ^{1}H NMR spectra of these compounds are entirely consistent with those of the proposed structures, and we have double checked the analyses several times. The analytical results vary up to 1% on **17c** and **21b** which may be indicative of decomposition and losses during the combustion process.

Pharmacological Data

Several of the bicyclic naphthalene-amidine adducts are being examined for analgesic and analgesic-antagonist activity in rodent screens. Initial results show interesting antagonist activity in some of these compounds. The results will be published elsewhere. The authors wish to thank Professor L. S. Harris at the Medical College of Virginia who is presently carrying out this testing.

Summary

A potentially useful new method for preparing benzofused heterobicyclic systems has been presented. It is not unlikely that this method can be developed for use with other types of potential "bis" bases, perhaps containing C-C-S, C-C-O, or mixed functionality, i.e., N-C-S, etc. A variety of methods are available for modifying nitronate and amidinium functionality similar to that obtained in the final products, and we are investigating the use of these methods on the compounds discussed here. We anticipate further use of such meta bridging reactions for preparation of a variety of new and useful ring systems.

Experimental Section

All melting points are uncorrected. ^{1}H NMR spectra were run on a JEOL MH-100 spectrometer with Me_4Si as an internal reference. Visible and ultraviolet spectra were recorded on a Perkin-Elmer Model 402 uv-visible spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer Model 237B infrared spectrophotometer.

Materials. TNB (Aldrich) was recrystallized three times from absolute ethanol and dried under vacuum at 60° for ~12 hr to yield white crystals, mp 121–122°. DNN (Aldrich), mp 145–147°, was used without further purification. TNN was prepared according to the procedure described by Fendler[26] and was recrystallized five times from benzene to give white crystals, mp 203–204°. Dimethylformamide (Fisher) was fractionally distilled after 2 hr of reflux over CaH_2. The fraction with bp 150–151° was collected and stored under nitrogen over 4A molecular sieves. Dimethyl sulfoxide (Fisher) was purified and stored in the same manner as DMF.

***N,N*-Dimethylacetamidine (6a).** Dry hydrogen chloride was passed through a mixture of 1.50 mol of dry acetonitrile and 1.55 mol of absolute ethanol in an ice bath until 1.60 mol was absorbed. After standing for 3 days, the resulting ethyl acetimidate hydrochloride became a solid mass. This mass was powdered in a mortar and pestle (in a drybox), and 12.25 g (0.1 mol) of the powder was dissolved in 10 ml of absolute ethanol. The solution was cooled to 0°, and 16.2 ml of 6.6 *M* dimethylamine (0.107 mol) in ethanol was then added. After 4 hr, the solution was filtered, and half the solvent was removed. Upon cooling, crystals precipitated. These were filtered off, and the filtrate was again condensed to give a second crop of crystals. The combined crystalline product was recrystallized twice from a 2:1 mixture of propanol:methanol. The resulting crystals were dried under vacuum at 80° for 10 hr to yield 10.3 g (85%) of *N,N*-dimethylacetamidine hydrochloride, mp 158–159° (lit.[27] 158–159°). The ir spectrum showed strong bands at 1625 and 1675. The ^{1}H NMR spectrum (DMSO-d_6) showed absorptions at δ 2.33 (s, 3 H), 3.16 (s, 3 H), 3.22 (s, 3 H), 8.88 (s, 1 H), and 9.74 (s, 1 H). The latter two NH absorptions were broad. Similar absorptions at δ 2.45, 3.24, 3.46, 9.20, and 9.95 were observed in $CDCl_3$. The salt is very deliquescent and hydrolyzes readily.

A solution of 18.87 g (0.155 mol) of *N,N*-dimethylacetamidine hydrochloride in 50 ml of dry methanol was mixed with a freshly prepared solution of 3.56 g (0.155 mol) of sodium in 50 ml of methanol. After cooling and filtering this solution, the filtrate was reduced to a volume of 25 ml on a rotary evaporator. This solution was fractionally distilled to yield 10.8 g (81%) of **6a,** bp 74° (67 mm). The ir spectrum of this material had a strong absorption at 1595 cm^{-1}. The ^{1}H NMR spectrum (DMSO-d_6) showed absorptions at δ 2.14 (s, 3 H), 3.02 (s, 6 H), and 5.78 (s, 1 H). Similar absorptions at δ 2.22, 3.12, and 6.30 were observed in $CDCl_3$.

***N,N*-Dimethylpropionamidine (6b).** This amidine was prepared by the same procedure as **6a.** The hydrochloride salt, mp 184–186°, obtained in 79% yield from reaction of propionitrile, dimethylamine, and HCl, had strong ir absorption at 1675 and 1625 cm^{-1}. The ^{1}H NMR spectrum (DMSO-d_6) showed absorptions at δ 1.16 (t, 3 H, J = 7 Hz), 2.72 (q, 2 H, J = 7 Hz), 3.18 (s, 3 H), 3.24 (s, 3 H), 8.98 (br s, 1 H), and 9.69 (br s, 1 H). It is extremely hygroscopic. If the reagents are not carefully dried, poor yields of product will result.

The free base **6b** was prepared by neutralization of the hydrochloride salt with sodium ethoxide as with **6a.** Fractional distillation of an ethanolic solution of **6b** gave an 80% yield, bp 61° (28 mm). The ir spectrum showed a strong absorption at 1590 cm^{-1}. The ^{1}H NMR spectrum (DMSO-d_6) showed absorptions at δ 1.04 (t, 3 H, J = 7 Hz), 2.28 (q, 2 H, J = 7 Hz), 2.88 (s, 6 H), and 6.16 (brs, 1 H).

***α*-Phenyl-*N,N*-dimethylacetamide (6c).** This amidine was prepared by the same procedure as **6a** and **6b.** The hydrochloride salt, mp 210–211°, obtained in 75% yield from reaction of benzylcyanide dimethylamine and HCl, had strong ir absorptions at 1635 and 1685 cm^{-1}. The ^{1}H NMR spectrum (DMSO-d_6) showed absorptions at δ 3.18 (s, 3 H), 3.22 (s, 3 H), 4.22 (s, 2 H), 7.57 (br s, 5 H), and 9.74 (br, 2 H). Similar absorptions at δ 3.16, 3.49, 4.34, 7.49, 10.02, and 10.73 were observed in $CDCl_3$.

The free base **6c** was prepared by neutralization of the hydrochloride salt with sodium ethoxide as with **6a** and **6b.** The crude oily product was fractionally distilled to give an 80% yield of **6c**, bp 93° (0.25 mm), which solidifies at about 25°. The solid was kept at 0° as it decomposed on warming as it melted. It has a strong ir absorption at 1595 cm^{-1}. The ^1H NMR spectrum (DMSO-d_6) showed absorptions at δ 2.89 (s, 6 H), 3.70 (s, 2 H), 6.16 (brs, 1 H), and 7.35 (m, 5 H).

Preparation of 8a. Addition of 0.0026 mol (0.225 g) of *N,N*-dimethylacetamidine in 10 ml of absolute ethanol to a solution of 0.0026 mol (0.557 g) of TNB in 50 ml of ethanol yielded an intensely colored solution. After standing for 12 days at room temperature, crystals were deposited on the bottom of the flask. These were filtered, washed with methanol and ether, and then dried with a diffusion pump at 70° for 8 hr to yield 0.631 g (81%) of **8a** as bright red crystals, mp 160–162°. The uv-visible spectrum (DMSO) showed maxima at 289, 460, and 567 nm. The ir spectrum (KBr) had strong absorptions at 3350, 3140, 1680, 1635, 1620, 1475, 1390, 1270, 1230, 1195, and 1150 cm^{-1}. The ^1H NMR spectrum and elemental analysis are recorded in Tables I and II.

Preparation of 8b. Addition of 0.0049 mol of *N,N*-dimethylpropionamidine in 25 ml of ethanol to 0.0049 mol of TNB in 50 ml of ethanol yielded a dark-orange solution which deposited red crystals after standing for 9 days. These were filtered, washed with anhydrous methanol, ether, and dried with a diffusion pump at 70° for 8 hr to provide 1.15 g (76%) of red crystals, mp 152–153°. The uv-visible spectrum (DMSO) showed maxima at 289, 460, and 567 nm. The ir spectrum (KBr) had strong absorptions at 3425, 3200, 1660, 1605, 1485, 1210, 1185, 1145, and 1045 cm^{-1}. The ^1H NMR spectrum and elemental analysis are recorded in Tables I and II.

Preparation of 17c. Addition of 10 ml of an ethanol solution of 0.001 mol of *N,N*-dimethylacetamidine to 0.001 mol of TNN in 350 ml of absolute ethanol yielded an intensely colored solution which was allowed to stand for 21 days at room temperature. The ethanol was then removed under reduced pressure, and the residue was added to 40 ml of dry methanol and stirred. The undissolved solid was filtered, washed with more methanol, then ether, and dried with a diffusion pump at 55° for 8 hr to yield 0.301 g (71%) of the product as a brown powder, mp 157–159°. The uv-visible spectrum (DMSO) showed maxima at 270, 485 (shoulder), and 530 nm. The ir spectrum (KBr) showed major bands at 1685, 1605, 1590, 1535, 1515, 1475, 1230, 1190, 1070, and 1015 cm^{-1}. The ^1H NMR spectrum and elemental analysis are recorded in Tables I and II.

Preparation of 17a. Addition of 0.0057 mol of *N,N*-dimethylacetamidine in 1 ml of DMSO to 0.0028 mol of DNN in 2 ml of DMSO at room temperature gave an intensely colored solution which was immediately cooled in an ice bath. After the exothermic reaction subsided, the mixture was stirred at room temperature for 24 hr to yield a red gel. Addition of this gel to 300 ml of anhydrous ether and stirring for a short while resulted in formation of a red powder. This was filtered and stirred with a fresh 300-ml portion of ether, then filtered and vacuum dried with a diffusion pump at 70° for 8 hr to give 0.933 g (89%) of the product as an amorphous powder, mp 136–138°. The uv-visible spectrum (DMSO) showed maxima at 273, 358, 368, and 545 nm. The ir spectrum (KBr) showed major bands at 3235, 3075, 1690, 1635, 1575, 1550, 1475, 1435, 1410, 1375, 1320, 1295, 1230, 1150, 1120, 1070, 1020, 1010, 945, 910, 870, 730, 715, and 670 cm^{-1}. The ^1H NMR spectrum and elemental analysis are recorded in Tables I and II.

Preparation of 10c. Addition of 50 ml of an ethanol solution of 0.0095 mol of α-phenyl-*N,N*-dimethylacetamidine to 0.0047 mol of TNB in 100 ml of ethanol yielded a dark-orange solution which was allowed to stand at room temperature for 10 days. The solvent was then removed on a rotary evaporator, and the remaining solid was added to 250 ml of anhydrous ether. This mixture was stirred for several hours, the insoluble powder was filtered off, and the procedure was repeated with a fresh portion of ether. The orange powder was then filtered and vacuum dried with a diffusion pump at 60° for 8 hr to give 2.1 g (88%) of product, mp 134.5–135.5°. The uv-visible spectrum (DMSO) showed maxima at 310 and 512 nm. The ir spectrum (KBr) showed major bands at 3140, 1640, 1575, 1570, 1540, 1400, 1345, 1325, 1170, 1115, and 980 cm^{-1}. The ^1H NMR spectrum and elemental analysis are recorded in Tables I and II.

Preparation of 9c. Addition of 0.0052 mol of α-phenyl-*N,N*-dimethylacetamidine in 1 ml of DMSO to 0.0051 mol of TNB in 1 ml of DMSO yielded a dark-orange solution which was stirred at 55° (water bath) for 1 hr and at room temperature for 11 hr. The resulting gel was added to 30 ml of anhydrous ether and stirred vigorously. The red solid which formed was filtered, added to a fresh 300-ml portion of ether, stirred for a short time, and again filtered. The resulting solid was then added to 100 ml of anhydrous methanol, stirred for several hours, filtered, and dried with a diffusion pump at 55° for 6 hr to yield 1.39 g of product (72.5%), mp 131–133°. The uv-visible spectrum showed maxima at 304 and 496 nm. The ir spectrum (KBr) showed major bands at 3275, 3215, 3115, 2995, 1635, 1560, 1535, 1475, 1400, 1365, 1350, 1265, 1215, 1115, 1075, 1035, 915, and 875 cm^{-1}. The ^1H NMR spectrum and elemental analysis are recorded in Tables I and II.

Preparation of 21d. A solution of 0.00234 mol of TNN in 0.7 ml of DMSO was warmed to 55°, and a slurry of 0.0047 mol of α-phenyl-*N,N*-dimethylacetamidine in 0.3 ml of DMSO was added. Heating was continued for an additional 30 min, and the mixture was allowed to cool to room temperature. After standing for 6 hr, the tarry product was added to 300 ml of ether, and the mixture was stirred vigorously. The tar was transformed to a powder which was mixed for several hours; the powder was filtered and dried with a diffusion pump at 60° for 8 hr to give 1.25 g (84%) of product, mp 90–92° with decomposition. The uv-visible spectrum showed maxima at 322, 348, and 553 nm. The ir spectrum (KBr) showed major bands at 3430, 3330, 2910, 1670, 1600, 1590, 1530, 1505, 1445, 1420, 1385, 1295, 1280, and 1175 cm^{-1}. The ^1H NMR spectrum and elemental analysis are recorded in Tables I and II.

It should be noted that this preparative procedure is very sensitive to traces of moisture in the solvents and reactants. In addition, the highest yields were obtained when very small reaction vessels were used with as little free air volume as possible. Running the reaction in larger reaction flasks, even with identical quantities, results in very poor yields.

Preparation of 19d. Solutions of 0.0093 mol of triethylammonium hydrochloride in 10 ml of methanol and 0.0091 mol of **28d** in 30 ml of methanol were combined and allowed to stand for 1 hr. The orange precipitate was then filtered, stirred with two successive 20-ml portions of methanol, refiltered, and dried with a diffusion pump at 70° for 8 hr to yield 0.147 g (34.5%) of the product, mp 154.5–156°. The uv-visible spectrum (DMSO) showed maxima at 305 and 522 nm. The ir spectrum showed major bands at 3380, 1640, 1595, 1550, 1525, 1490, 1420, 1375, 1320, 1280, 1245, 1180, 1135, 1100, and 955 cm^{-1}. The ^1H NMR and elemental analysis are recorded in Tables I and II.

Preparation of 21b. A solution of 0.003 mol of DNN in 1.5 ml of DMSO was warmed to 55°. A slurry of 0.0064 mol of α-phenyl-*N,N*-dimethylacetamidine in 0.5 ml of DMSO was then added. After 15 min, the mixture was cooled to room temperature and allowed to stand for 3 days. The reaction mixture was then added to 300 ml of ether, and the heterogenous mixture was stirred vigorously. The resulting pink precipitate was filtered, redissolved in 30 ml of ethanol, and again precipitated by addition of ether. Filtration and drying of the precipitate with a diffusion pump at 65° for 6 hr yielded 1.33 g (80%) of product, mp 112–114°. The uv-visible spectrum (DMSO) showed a single maximum at 351 nm. The ir spectrum (KBr) showed major bands at 1690, 1630, 1530, 1460, 1440, 1385, 1370, 1190, 1125, 1110, 990, and 750 cm^{-1}. The ^1H NMR and elemental analysis are recorded in Tables I and II.

Preparation of 19b. Solutions of 0.0094 mol of triethylammonium hydrochloride in 10 ml of methanol and 0.0092 mol of **21b** in 30 ml methanol were combined, and the mixture was allowed to stand at room temperature for 24 hr. Yellow crystals were formed in the solution, and these were filtered off. The filtrate was concentrated, and a second crop of crystals was obtained. These crystals were pulverized and stirred with anhydrous methanol. After repeated washing with fresh methanol, the powder was dried with a diffusion pump at 60° for 6 hr to yield 0.324 g (92%) of product, mp 140–141°. The uv-visible spectrum (DMSO) showed a single maximum at 357 nm. The ir spectrum (KBr) showed major bands at 3260, 1625, 1560, 1550, 1475, 1425, 1415, 1375, 1365, 1355, 1275, 1230, 1200, 1125, 1110, 1065, 1035, 995, 970, 905, 840, 815, 795, 750, and 695 cm^{-1}.

The compound is extremely insoluble, and a satisfactory ^1H NMR spectrum could not be obtained. Heating DMSO solutions of **19b** resulted in disproportionation to 1 equiv each of DNN and **21b**. In the ^{1}H NMR spectra of these solutions, a peak corresponding to 0.5 equiv of methanol was also observed. The elemental analysis is recorded in Table II.

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Synthesis of Metabolites of Δ^9-Tetrahydrocannabinol

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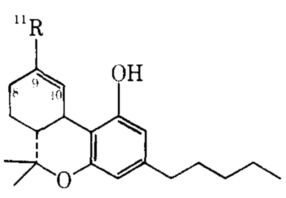
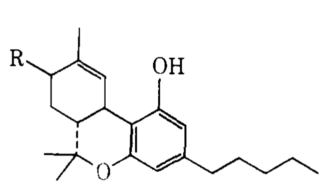
Abstract: New syntheses of the human metabolites, 11-hydroxy-, 8α-, and 8β-hydroxy-Δ^9-THC, and the first syntheses of the metabolites, 8α,11- and 8β,11-dihydroxy-Δ^9-THC, and 11-nor-Δ^9-THC-9-carboxylic acid, are described. The base-induced epoxide–allylic alcohol rearrangement, followed by SN′ displacement, provides a new method of derivatizing the allylic 11-methyl group of Δ^9-THC.

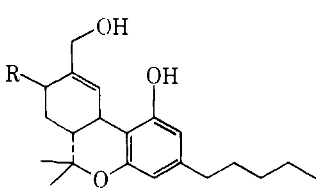
Δ^9-Tetrahydrocannabinol (Δ^9-THC, **1a**), the psychotomimetic principle of marihuana,[1] is metabolized via allylic hydroxylation.[2] Three monohydroxy (**1b, 2a, 2b**), two dihy-



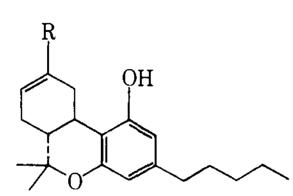
1a, R = CH_3
b, R = CH_2OH
c, R = COOH
d, R = CH_2Br



2a, R = α-OH
b, R = β-OH
c, R = O



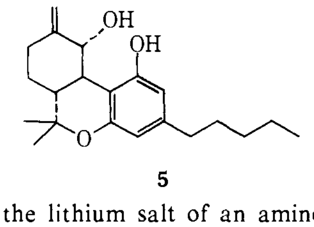
3a, R = α-OH
b, R = β-OH



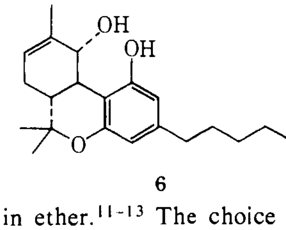
4a, R = CH_3
b, R = CH_2OH

droxy (**3a, 3b**), and one carboxy (**1c**) metabolites have already[3] been positively identified in man.[4] Of these, **1b, 2a,** and **2b** are bioactive and probably contribute in part to the activity profile of marihuana.[5] Synthetic sources of these metabolites, urgently sought to aid pharmacological studies, have been restricted by a paucity of regioselective methods of functionalizing the allylic 11-methyl group of Δ^9-THC.[6] Procedures which satisfactorily provide Δ^8-THC (**4**) metabolites[2,7] work poorly when applied to the metabolites of Δ^9-THC[8] because of the instability of the 9,10-double bond and the ease of oxidation and aromatization.[7f] As a result, no syntheses of **1c, 3a,** and **3b** have been reported, and syntheses of the key[5] metabolite **1b** have suffered from low yields and difficult separations.[8] Here we describe new regioselective routes to all six human metabolites of Δ^9-THC, starting with the synthesis of 11-hydroxy-Δ^9-THC (**1b**).

Δ^9-THC acetate was quantitatively converted to its known α-epoxide,[10] which was isomerized to a mixture of the allylic alcohols **5** and **6** in >80% yield by treatment with



5



6

the lithium salt of an amine in ether.[11-13] The choice of amine determined the ratio **5**/**6** (e.g., C_6H_5NH-*i*-Pr or Et_2NH, 0.2; *i*-Pr_2NH, 2,2,6,6-tetramethylpiperidine, or $(Me_3Si)_2NH$, 1.0; Me_3SiNH-*t*-Bu, 4.0), the bulkier sub-