A CORRELATION OF THE CHEMISTRIES OF TWO THIENOPYRIDINES WITH THOSE OF BENZO[b]THIOPHENE AND QUINOLINE

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Abstract.--All of the presently known chemistries (including S_E and S_N reactions, heteroatomic oxidations, reactions of ring substituents, and reactions of N- and S-oxides) of the thieno[2,3-b]pyridine and thieno[3,2-b]pyridine (TP) systems are shown to be interpretable as amalgamations of the chemistries of the reference compounds benzo[b]thiophene (BT) and quinoline (Q). Three general relationships are noted, viz. (a) cases where all systems (TP, BT, and Q) give reactions which are consistent with one another, (b) cases where the TP system gives reaction analogous to that of the BT or Q system only, and (c) cases where the TP system gives dual reactions as if it were a mixture of the BT and Q systems. In particular, isosteric relationships are commonly observed. Electronic interactions between the rings in TP are considered.

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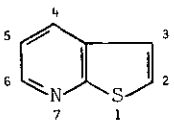
1. INTRODUCTION

Identifiable interring effects may be expected for bicylic molecules in which the two rings can be readily distinguished due to an unsymmetrical substitution pattern (as in 1-nitronaphthalene) or a difference in the parent rings *per se* (as in azulene or quinoline). There is considerable current interest in those effects which arise from the fusion of two non-equivalent monoheterocycles. In fact, Hartough and Meisel[1] were the first to note in a publication (1954) that thienopyridine (TP) systems should be particularly pertinent for a systematic study of the effects of ring interactions on the substitution patterns of the monocyclic components (thiophene and pyridine). Both thiophene and pyridine have recognized aromatic character with resonance energies somewhat less than benzene, but with markedly different properties in substitution.[2] Thiophene (a π-excessive compound) undergoes electrophilic substitution more readily than does benzene (predominantly in the 2- and 5-positions), but it rarely gives nucleophilic substitution unless the ring contains electron-attracting substituents.[3,4] Contrariwise, pyridine (a π-deficient compound) resists electrophilic substitution to a remarkable degree unless the ring contains electron-releasing substituents, but it undergoes nucleophilic substitution readily (at the 2- and 4-positions).[3,5] Both monocycles are susceptible to free-radical attack. Also in both cases the heteroatom retains an electron pair which is not needed to complete the set of six aromatic π-type electrons. These non-bonding electron pairs permit the formation of salts (more readily in the case of pyridine) and of heteroatomic oxides, wherein chemical properties are considerably modified from those of the parent systems.

Extensive investigation of the chemistries of the thienopyridines was infeasible until the period of 1968-1972, when practical syntheses for all six of the possible parent compounds were reported in the literature.[6-10] Two reviews of the synthetic procedures and reactions of the TP systems have already appeared,[11,12] but neither has attempted to correlate their chemistries with interring effects or the chemistries of other known systems. It is the purpose of this paper to present an interpretative review of the chemistries of thieno[2,3-*b*]pyridine (1) and thieno[3,2-*b*]pyridine (2) which have been reported to date from these points of view and to indicate some areas of interest which remain to be explored. With few exceptions, the results described have been obtained in my research group at the University of Oregon.



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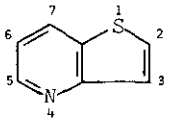

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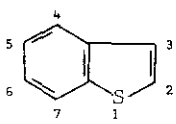

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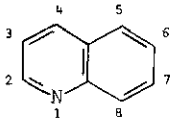

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2. A QUALITATIVE CORRELATIONAL MODEL

It is the thesis of this paper that the interring effects and the chemistries of 1 and 2 represent an amalgamation of those of benzo[b]thiophene (BT) (3) and quinoline (Q) (4). To apply this interpretation one should remember that 1 and 2 are isosteres of Q (wherein positions 2 and 3 of 1 correspond to 6 and 5 of 4 and positions 2 and 3 of 2 correspond to 7 and 8 of 4, respectively), as well as isosteres of BT (where ring positions correspond directly). In some cases (e.g. nitration in mixed acid) the positions of monosubstitution in 1 or 2 (TP), BT, and Q are all consistent with one another. In others (e.g. heteroatom oxide formation), TP may react either in the manner of BT alone or Q alone. As a third class of transformations (in particular, treatment with RLi) 1 gives dual reactions as if it were a mixture of BT and Q together.

An electronic basis for the correlations of 1-4 was provided from observations on dipole moments.[13] It was shown that one can calculate to an accuracy of 6% or less the measured dipole moments of 1 (2.81 D) and 2 (1.80 D) from those reported for BT and Q, as reference compounds. This calculation involves the vector addition of the dipole moments of BT and Q for a configuration wherein the molecules are superimposed in the same plane and oriented so as to bring the heteroatoms into the correct syn (for 1) or anti (for 2) geometries.

That the sulfur atom serves to withdraw σ-type electronic charge from the nitrogen atom by inductive effect is apparent from the fact that 1 (pK_a = 2.75) and 2 (pK_a = 4.35) are less basic toward the proton than is Q (pK_a = 4.9).[14] Unexpectedly, Hückel molecular orbital calculations indicate that π-electronic densities on the heteroatoms in both 1 and 2 are identical (q_r = 1.32) and greater than on any of the carbon atoms in either ring.[6,15] This represents the drift of 0.68 π-electronic charge away from S and of 0.32 π-electronic charge onto N (as compared to the situation in a hypothetical, completely π-localized molecule). Though the pyridine ring seems to gain a net π-electronic charge of 0.31 units from the thiophene ring, one anticipates no major upset in the

relative susceptibilities of the two rings toward nucleophilic and electrophilic attacks. Thus, the predicted position of preference for electrophilic substitution on carbon (as based either on q_r or on superdelocalizability) follows the orders 3 >> 2 for 1 and 2, while that for nucleophilic substitution shows the orders 4 > 6 for 1 and 7 > 5 for 2. As will be noted later, experimental results for S_E reactions are consistent with these predictions. However, for reaction of 1 with RLi, the only nucleophilic substitution thus far conducted on the parent TP, the R substituent enters position 6 (α to N) rather than 4 (γ to N). In contrast, CNDO calculations[16] indicate that the nitrogen atom should acquire both π and σ electronic charge, while the sulfur atom should be depleted in both of these. The frontier electron density index for S_E follows the partially correct orders 3 >> 4 for 1 and 3 >> 7 for 2; but the frontier orbital density index for S_N shows the incorrect order 2 >> 6 for 1, as well as the unlikely order 2 >> 3 for 2. Pariser-Parr-Pople calculations[16] are consistent with the CNDO and Hückel ones in showing a shift of π-electronic charge away from S and onto N. Consideration of free-radical substitutions into 1 and 2 is unwarranted at this time since no experimental data are yet available on such reactions.

3. ELECTROPHILIC SUBSTITUTION

In Table 3.1 are presented the known examples of electrophilic substitution into the TP system (mainly 1), for which similar reactions have been reported in the Q and BT systems. Three major processes (viz. nitration, halogenation, and acid-catalyzed deuteriation) have been studied thus far. Only one mononitro product, the 3-isomer, was identified from nitration of either 1 or 2 by means of nitric and sulfuric acids (examples 1 and 2, see also ref. 29). The corresponding reaction (no. 4) with quinoline produces a mixture of mononitro isomers (5- and 8-) which are isosteres of 3-nitro-1 and 3-nitro-2 (respectively). It is believed that protonated heteronitrogen species are involved in these nitration reactions,[31] whereby electrophilic attack is directed toward the electrically uncharged ring. Since BT lacks a nitrogen atom and also undergoes sulfonation[32] in the presence of H_2SO_4, substrate BT is nitrated in HOAc or Ac_2O as solvent, instead of in H_2SO_4.[32] Under these less stringent nitration conditions, where neither ring is deactivated toward S_E reaction, substitution at C-3 is still the main reaction (no. 3 and ref. 32), but other isomers (from

Table 3.1. Comparative Electrophilic Substitutions into TP (1 or 2), BT (3), and Q (4) Systems.

Example No.	Substitution Process	Substrate Used	Reagent(s) and Reaction Conditions	Position(s) of Substitution and Yield[a]	Reference(s)
1	Nitration	1	HNO_3, H_2SO_4, 110°	3 (55)	15
2	Nitration	2	HNO_3, H_2SO_4, 65°	3 (48)	15
3	Nitration	BT	HNO_3, HOAc, 10°	3 [47], 4 [43], 6 [9]	17
4	Nitration	Q	HNO_3, H_2SO_4, 0°	5 (24), 8 (22)	18
5	Nitration	3-Br-1	HNO_3, H_2SO_4, 110°	2 (47)	19
6	Nitration	3-Br-BT	HNO_3, HOAc, 15°	2 (33), 4 (7)	17
7	Chlorination	1	Cl_2, H_2SO_4, Ag_2SO_4, 90°	3 (40)	19
8	Chlorination	Q	Cl_2, H_2SO_4, Ag_2SO_4, 22°	5, 8, 5,8	20
9	Bromination	1	Br_2, H_2SO_4, Ag_2SO_4, 40°	3 (27)	19
10	Bromination	Q	Br_2, H_2SO_4, Ag_2SO_4, 22°	5 (28), 8 (29), 5,8 (43)	21
11	Iodination	1	I_2, H_2SO_4, Ag_2SO_4, 125°	3 (30)	19
12	Iodination	Q	I_2, H_2SO_4, Ag_2SO_4, 175°	5, 8, 5,8	22
13	Chlorination	1	Cl_2, $CHCl_3$, H_2O, reflux	3 (27), 2,3 (40)	19
14	Chlorination	BT	Cl_2, CCl_4, 22°	2 [3], 3 [69], 2,3 [28]	23,24
15	Oxidochlorination	1	Cl_2, $CHCl_3$, H_2O, 10°	2,3 [60], 2,3,3 [40]	25
16	Oxidochlorination	BT	t-BuOCl, 95% t-BuOH, 20°	2,3 (60)	26
17	Bromination	1	Br_2, CCl_4, H_2O	2,3 (17)	6
18	Bromination	BT	Br_2, CCl_4, 18°	3 (92)	27
19	Bromination	1	Br_2, K_2HPO_4, $NaHCO_3$, $MgSO_4$, $CHCl_3$, reflux	3 (57)	19

Table 3.1. (continued)

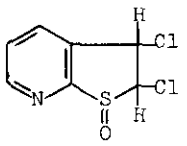
Example No.	Substitution Process	Substrate Used	Reagent(s) and Reaction Conditions	Position(s) of Substitution and Yield[a]	Reference(s)
20	Bromination	BT	Br_2, NaOAc, $CHCl_3$, 22°	2 [3], 3 [87], 2,3 [10]	23,28
21	Deuteriation	1	D_2SO_4, 100°, pH 0	3 > 2	29
22	Deuteriation	BT	D_2SO_4, 100°, pH 0	3 ≃ 2 (estimated)	29
23	Deuteriation	Q	D_2SO_4, 100°, pH 0	8 > 5	29,30

[a]Numbers in parentheses are isolated yields (%); those in brackets are analytical yields [%], as based on the total identified products.

nitration in the benzene ring) are formed as well. Consistent with this line of reasoning is the observation that nitration of 3-bromo-1 in mixed acid also gives substitution (at C-2) into the non-protonated ring (no. 5), while nitration of 3-bromo-BT in HOAc gives mainly 2-substitution but also appreciable 4-substitution (no. 6). Analogously, 3-chloro-1 and 3-iodo-1 direct acid-catalyzed nitration to C-2.[19]

Chlorination, bromination, and iodination of Q in the presence of H_2SO_4-Ag_2SO_4 (protonated nitrogen species) give mixtures of 5-halo, 8-halo, and 5,8-dihalo derivatives (nos. 8, 10, and 12). This sulfate mixture likewise effects halogenation of 1 at C-3, isosteric to C-5 of Q (nos. 7, 9, and 11). Similar halogenation of 2 (wherein C-3 is isosteric to C-8 of Q) has not yet been investigated.

For halogenation of BT one not only avoids the use of added strong acid but may even conduct the reaction in the presence of a buffer (to absorb HX formed in situ). Similar methodologies for chlorination and bromination have also been investigated for 1. Direct chlorination (examples 13 and 14) occurs at C-2 and C-3 in both systems, with the latter position of greater significance. Besides direct substitution of chlorine one also finds both addition of Cl_2 to the 2,3-double bond and oxidation of the heteroatomic sulfur when H_2O is present in the reaction mixture. Thus, 1 yields stereoisomers of 5 and 6 while BT forms stereoisomers of 7 under oxidochlorination conditions (nos. 15 and 16).



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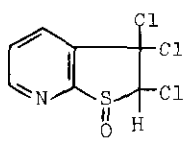

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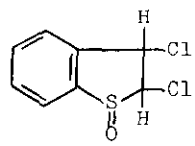

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Direct bromination of BT in neutral, anhydrous medium (no. 18) under carefully controlled conditions gives a high yield of 3-bromo product. However, 2,3-dibromination[32] and even a little 2-bromination also occur, particularly in buffered solution (no. 20). While direct bromination studies on 1 under strictly comparable conditions to those used with BT have not been made, both 3-bromo and 2,3-dibromo derivatives were obtained (nos. 17 and 19). Example 19 was conducted under conditions designed to keep both HX and H_2O concentrations low. The strong orientation toward electrophilic substitution at C-3 is

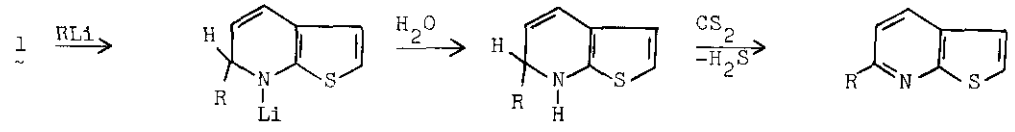
apparent in this case.

In deuteriation by means of D_2SO_4 (nos. 21-23) the relative rates for reaction fall in the order BT (at C-3 and C-2) >> 1 (at C-3 and C-2) > Q (at C-8 and C-5). Again substitution patterns are analogous in the three systems.

As expected, in reactivity toward electrophilic substitution (and in accordance with the direct measurements on rates of deuteriation[29]), 1 occupies a position intermediate between those of BT and Q. Moreover, the experimentally observed order of reactivity in S_E of 3 >> 2 for 1 and the nitration of 2 at C-3 are consistent with predictions as based on Hückel MO calculations.

4. LITHIATION REACTIONS

The only nucleophilic substitution reaction to which the parent TP 1 has been subjected is treatment with organolithium compounds, RLi. Comparison of those experiments with analogous reactions in the Q and BT systems is made in Table 4.1. Typically, when treated with RLi, BT undergoes direct exchange of Li for H at C-2 to give an intermediate which can be transformed into various 2-substituted BT compounds (no. 25). Contrariwise, Q adds RLi to the C-N double bond to form (after hydrolysis and dehydrogenation) a 2-(R-substituted) quinoline (no. 28). As is apparent from examples 24, 26 and 27 treatment of 1 with RLi gives either 2-lithiation (as with BT) or 6-alkylation (as with Q), or a mixture of both processes. Lithiation at C-2 is favored by a low reaction temperature and the presence of N,N,N',N'-tetramethylethylene diamine (TMEDA), while addition of RLi to the C-N double bond is fostered by refluxing in ether solution. The CS_2 in examples 26 and 27 serves as a dehydrogenating agent for the proposed intermediate 6-alkyl-6,7-dihydroquinoline (8), thus:



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Examples 29-31 illustrate analogous cases of lithium-bromine exchange as a route to derivatives (in the 1, Q, and BT systems) which are not available by lithium-hydrogen exchange or by addition to a C-N double bond.

While reaction of 1 with RLi is not the best possible test of the position of nucleophilic attack therein,[38] results are consistent with expectations for

Table 4.1. Comparative Lithiation Reactions in the Thieno[2,3-b]pyridine (1), BT (3), and Q (4) Systems

Example No.	Substrate Used	RLi Used and Reaction Conditions	Reagent(s) Added to Intermediate	Substituent Introduced, Yield (%)	Reference
24	1	n-BuLi, TMEDA, -70° hexane	Me_2NCHO	2-CHO (66)	33
25	BT	n-BuLi, ether, reflux	Me_2NCHO	2-CHO (62)	34
26	1	n-BuLi, ether, reflux	H_2O, then CS_2	6-n-Bu (47)	6
27	1	MeLi, ether, -25°	D_2O, then CS_2	6-Me (11), 2-D (ca. 40)	6
28	Q	n-BuLi, ether, -35°	H_2O	2-n-Bu (94)	35
29	3-Br-1	n-BuLi, ether, -70°	Me_2NCHO	3-CHO (77)	33
30	3-Br-BT	n-BuLi, ether, -70°	Me_2NCHO	3-CHO (74)	36
31	5-Br-Q	n-BuLi, THF-ether, -70°	Me_2NCHO	5-CHO (70)	37

S_N to occur at either C-4 or C-6, as predicted from Hückel MO calculations.

5. HETEROATOMIC OXIDATION

Both Q and BT undergo electrophilic heteroatomic oxidation (to the N-oxide and S,S-dioxide, respectively) by means of H_2O_2 and HOAc (nos. 34 and 39, Table 5.1). Thienopyridines 1, 2, and 4-chloro-1, however, react only in the manner of Q (i.e. to form N-oxides) with this reagent (nos. 32, 33, and 35). In fact, various tricyclic thienopyridine compounds react likewise.[40] In order to obtain the S,S-dioxide (i.e. the sulfone) of a thienopyridine, the reagent of choice is acidified NaOCl, probably to give HOCl as the active oxidizing agent (nos. 36 and 37). Acidified NaOCl also produces the sulfone of BT (no. 38). Likewise, in analogy to the BT system, TP S-oxides (i.e. sulfoxides) are known only as their 2,3-dihydro derivatives[32] (see footnote a, Table 5.1).

The observed selectivity in these oxidations has been interpreted (see ref. 25) in terms of the principle of Hard and Soft Acids and Bases, whereby the order of hardness for the acids is

$$\overset{\delta+\ \delta-}{HO\text{-}OH} > \overset{\delta+\ \delta-}{Cl\text{-}OH} > \overset{\delta+\ \delta-}{Cl\text{-}Cl} \quad ,$$

and that for the basic entities is

azine N > thiole S > 2,3-C=C- , 2,3-dihydrothiole S.

6. REACTIONS OF N-OXIDES

Table 6.1 presents examples of analogous reactions which occur in the quinoline N-oxide (10) and thieno[2,3-b]pyridine N-oxide (9) systems. Both N-oxides undergo selective nitration in the γ position (to the heteroatomic N) in mixed nitric-sulfuric acids (nos. 40 and 41). With HNO_3-HOAc, however, compound 9 gives nitration β to the heteroatomic N. While no attempt to study the effect of the same reagent mixture on 10 has been reported, β-nitration of 10 is observed from treatment with acetyl nitrate (formed in situ in example 43) or benzoyl nitrate.[45] The 4-nitro N-oxides in both the Q and 1 systems are transformed into 4-chloro N-oxides upon treatment with acetyl chloride (nos. 45 and 44), and the 4-chloro substituents are, in turn, replaceable by dialkylaminoalkylamino chains (nos. 47 and 46). Thus, both 9 and 10 undergo similar S_E (nitration) and S_N (chlorodenitration and alkylaminodechlorination)[45,52] reactions with retention of the N-oxide function.

Table 5.1. Comparative Heteroatomic Oxidations in TP (1 or 2), BT (3), and Q (4) Systems.

Example No.	Substrate Used	Reagent(s) and Reaction Conditions	Oxide Product[a]	Product Yield, %	Reference
32	1	30% H_2O_2, HOAc, 55°	N-oxide (9)	53	39
33	2	30% H_2O_2, HOAc, 55°	N-oxide	32	40
34	Q	29% H_2O_2, HOAc, 68°	N-oxide (10)	92	41
35	4-Cl-1	30% H_2O_2, HOAc, 55°	4-chloro-N-oxide	37	42
36	1	HCl, NaOCl, 22°[b]	S,S-dioxide	37	43
37	2	HCl, NaOCl, 22°[b]	S,S-dioxide	34	43
38	BT	HCl, NaOCl, 22°[b]	S,S-dioxide	26	43
39	BT	30% H_2O_2, HOAc, reflux	S,S-dioxide	95	44

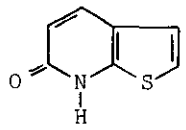
[a]For processes of oxidochlorination see Table 3.1, nos. 15 and 16. [b]Using the molecular ratio of substrate:HCl:NaOCl = 1:2:2.

Table 6.1. Comparative Reactions of Thieno[2,3-b]pyridine 7-Oxide (9), Quinoline 1-Oxide (10), and Allied N-Oxides.[a]

Example No.	Substrate Used	Reagent(s) and Reaction Conditions	Product(s) Formed and Yield (%)	Reference
40	9	96% H_2SO_4, 70% HNO_3, 90-120°	4-nitro-1 N-oxide (11) (50)	39
41	10	96% H_2SO_4, 60% HNO_3, 68°	4-nitro-Q N-oxide (12) (67)	41
42	9	HOAc, 70% HNO_3, 120°	5-nitro-1 N-oxide (54)	39
43	10	AcCl, $AgNO_3$, $CHCl_3$, -20° to +22°	3-nitro-Q N-oxide (21-32), 3,6-dinitro-Q N-oxide (6-10), 6-nitro-Q N-oxide (0-1)	46
44	11	AcCl, reflux	4-chloro-1 N-oxide (13) (81)	39
45	12	AcCl, 0-40°	4-chloro-Q N-oxide (98)	41
46	13	$R_2N(CH_2)_nNH_2$, 100°	4-$NH(CH_2)_nNR_2$-1 N-oxide (23-60)	39
47	14[b]	$Et_2N(CH_2)_3NH_2$, EtOH, a little HCl, reflux	7-chloro-4-$NH(CH_2)_3NEt_2$-Q N-oxide (60)	47
48	9	$POCl_3$, reflux	4-chloro-1 (54); 6-chloro-1 (31)	42
49	10	$POCl_3$, reflux	4-chloro-Q/2-chloro-Q = 1.7	48
50	9	Ac_2O, reflux; then alkaline hydrolysis	thienopyridone 15 (13); 5-hydroxy-1 (4)	42
51	10	Ac_2O, reflux	carbostyril (16) (20-90), byproducts (0-35)	49
52	9	KCN, CH_2Cl_2-H_2O, benzoyl chloride, 22°	6-cyano-1 (46)	50
53	10	KCN, H_2O, benzoyl chloride, > 20°	2-cyano-Q (ca. 100)[c]	51

[a]Differences in extent of hydration (if any) or the salt used are ignored in these reactions, except in calculations of yield. [b]Compound 14 is 4,7-dichloroquinoline 1-oxide. [c]Crude reaction product.

Examples 48-53 illustrate analogous cases in the systems 9 and 10 of S_N reactions with attendant de-N-oxidation. In nos. 48 and 49 $POCl_3$ effects substitution by Cl in both γ and α positions (ratio of isomers 1.7). α-Pyridones (15 and 16) are the main products isolated from refluxing with Ac_2O (followed by



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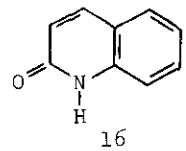

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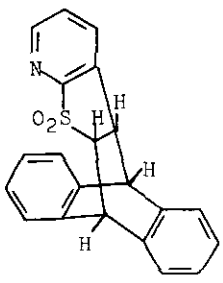
hydrolysis), and only α-cyano derivatives result from the Reissert-Henze reaction with benzoyl chloride and KCN.

7. REACTIONS OF S,S-DIOXIDES

In Table 7.1 are listed analogous Diels-Alder condensations found for the sulfones from 1 and BT. Both react as dienophiles (nos. 54-57) with anthracene and naphthacene to form the 1:1 adducts 19-22. Compound 17 also reacts with



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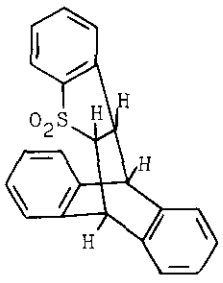

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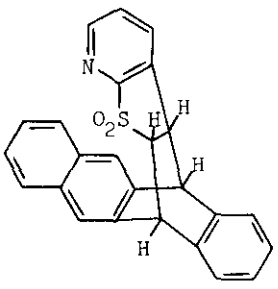

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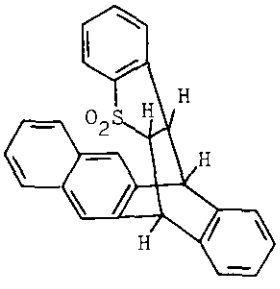

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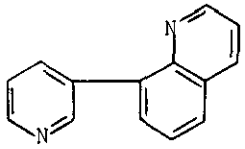
exo or endo

the diene furan to give both exo and endo adducts.[43] Considerable interest has been generated by the self-condensation (proposed as a Diels-Alder dimerization, plus thermal loss of a molecule of SO_2) of 18 (no. 59) to yield the dihydrosulfone 24. Compound 17, likewise, undergoes dimerization to form (after loss of two molecules of SO_2) the pyridylquinoline 23 (no. 58).



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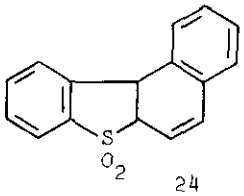

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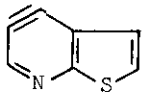
Table 7.1. Comparative Diels-Alder Condensations Involving Thieno[2,3-b]pyridine 1,1-Dioxide (17) or Benzo-[b]thiophene 1,1-Dioxide (18).

Example No.	Reactants Used	Reaction Conditions	Product Formed and Yield (%)	Reference
54	17 and anthracene	refluxing xylene	adduct 19 (45)	43
55	18 and anthracene	refluxing o-$C_6H_4Cl_2$	adduct 20 (83)	53
56	19 and naphthacene	refluxing xylene	adduct 21 (29)	43
57	20 and naphthacene	refluxing xylene	adduct 22 (94)	53
58	17 only	refluxing xylene	8-(3-pyridyl)-Q (23) (25), SO_2	43
59	18 only	butyl carbitol, 220°	24 (74), SO_2	54

8. TRANSFORMATION OF RING SUBSTITUENTS

Tables 8.1 and 8.2 list various chemical transformations of substituents present on the thiophene and pyridine rings (respectively) of TP and comparison with results from analogous reactions in the BT and Q systems. Insofar as data could be garnered from the literature the Q and BT substrates selected are isosteres of the TP ones. Examples 60 and 61 involve the direct reductive acetylation of nitro groups in 1 and BT, while 62-65 concern reduction with Sn (or $SnCl_2$) and HCl of nitro groups to amino groups. Reduction of the isosteres 3-nitro-1 and 5-nitro-Q occurs without attendant side reaction, while isosteric 3-nitro-2 and 8-nitro-Q undergo both reduction and chlorination in the process. In other examples 3-bromo groups in 1 and BT are replaceable by CN through reaction with CuCN (nos. 66 and 67); cyano groups react with Grignard reagents to form ketones (nos. 68-70); acetyl derivatives undergo the Wolff-Kishner reaction (nos. 71 and 72) and oximation (nos. 73-75); and the Beckmann rearrangement takes place on the oximes (nos. 76-78).

For substituents in the pyridine ring of 1 there are examples of hydration of the cyano group to give carboxamides by means of alkaline H_2O_2 (nos. 79 and 80) and copper-promoted alkylaminodechlorination (nos. 81 and 82) at a position α to the heteroatomic N (or an isosteric position in BT). For the 5-acetyl substituent in 1 (β to the ring N) there are analogous cases of oximation (examples 83 and 84) and Willgerodt reaction (nos. 85 and 86), as well as the Beckmann rearrangement[66] (of 28, no. 83). The 5-amino group (in 1) can be diazotized and replaced by CN (nos. 87 and 88), as well as Br or Cl (Sandmeyer reactions).[66] Hydrolysis of the diazonium compound produces the β-hydroxy derivative (nos. 89 and 90); while treatment of the β-bromo compound with KNH_2 in liquid ammonia produces a mixture of the β- and γ-amino compounds (nos. 91 and 92), probably via the pyridyne-type intermediates 29 and 30, respectively.



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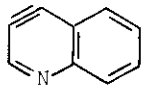

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An OH function (per se, or as its keto tautomer) α or γ to the heteroatomic N is replaceable by Cl by means of heating with $POCl_3$ (with or without PCl_5 added) (nos. 93-96).

Table 8.1. Comparison of Reactions of Substituents in the Thiophene Ring of TP (1 or 2) with Those of Substituents in Isosteric or Analogous BT and Q Compounds

Example No.	Substrate Used	Reagent(s) and Reaction Conditions	Product(s) Formed and Yield (%)	Reference(s)
60	3-nitro-1	HOAc, Ac_2O, Fe, 55°	3-acetylamino-1 (82)	55
61	3-nitro-BT	HOAc, Ac_2O, Fe, 55°	3-acetylamino-BT (80)	55
62	3-nitro-1	conc. HCl, Sn, 22°	3-amino-1 (39)	15
63	5-nitro-Q	conc. HCl, $SnCl_2$, > 20°	5-amino-Q (64)	56
64	3-nitro-2	conc. HCl, Sn, 26°	2-chloro-3-amino-2 (98)[a]	15
65	8-nitro-Q	conc. HCl, $SnCl_2$, > 20°	5-chloro-8-amino-Q (20), 7-chloro-8-amino-Q (*ca.* 38)	15,57
66	3-bromo-1	CuCN, Me_2NCHO, reflux	3-cyano-1 (45)	19
67	3-bromo-BT	CuCN, C_5H_5N, 215°	3-cyano-BT (78)	58
68	3-cyano-1	MeMgI, Et_2O-C_6H_6, reflux	3-acetyl-1 (18)	19
69	3-cyano-BT	MeMgI, Et_2O, reflux	3-acetyl-BT (15)	59
70	5-cyano-Q	*o*-MeC_6H_4MgBr, Et_2O-C_6H_6, reflux	5-(*o*-Me-benzoyl)-Q (33)	60
71	2-acetyl-1, 2-acetyl-2 [b]	$NH_2NH_2 \cdot H_2O$, KOH, diethylene glycol, reflux	2-ethyl-1, 2-ethyl-2 [b] (74)	6
72	2-acetyl-BT	NH_2NH_2, H_2O, KOH, diethylene glycol, reflux	2-ethyl-BT (84)	61
73	2-acetyl-1	$NH_2OH \cdot HCl$, C_5H_5N, EtOH, reflux	2-acetyl-1 oxime (25) (80)	15
74	2-acetyl-2	$NH_2OH \cdot HCl$, NaOAc, EtOH-H_2O, reflux	2-acetyl-2 oxime (26) (96)	15
75	3-acetyl-BT	"standard procedure"	3-acetyl-BT oxime (27)	62
76	oxime 25	C_6H_6, PCl_5, reflux	2-acetylamino-1 (77)	15

Table 8.1. (continued)

Example No.	Substrate Used	Reagent(s) and Reaction Conditions	Product(s) Formed and Yield (%)	Reference(s)
77	oxime 26	tetrahydrofuran, PCl_5, 0°	2-acetylamino-2 (45), 2-[2-(N-methyl)carboxamide] (8)	15
78	oxime 27	PCl_5, Et_2O, 22°	3-acetylamino-BT (89)	62

[a]Crude yield. [b]Mixture of isomers.

Table 8.2. Comparison of Reactions of Substituents in the Pyridine Ring of TP (1) with Those of Substituents in Isosteric or Analogous BT and Q compounds

Example No.	Substrate Used	Reagent(s) and Reaction Conditions	Product(s) Formed and Yield (%)	Reference
79	6-cyano-1	NaOH, 12% H_2O_2, ethanol, 55°	1-(6-carboxamide) (68)	50
80	6-cyano-BT	NaOH, 3% H_2O_2, 22°	BT-(6-carboxamide) (49)	63
81	6-chloro-1	$Et_2N(CH_2)_3NH_2$, Cu, 168°, sealed tube	6-[$Et_2N(CH_2)_3NH$]-1 (58)	64
82	2-chloro-Q	n-$BuNH_2$, Cu, 170°, sealed tube	2-n-Bu-Q (78)	65
83	5-acetyl-1	$NH_2OH \cdot HCl$, C_5H_5N, EtOH, reflux	5-acetyl-1 oxime (28) (91)	66
84	5-acetyl-BT	$NH_2OH \cdot HCl$, KOAc, EtOH, reflux	5-acetyl-BT oxime (86)	67
85	5-acetyl-1	S_8, morpholine, reflux	1-(5-acetothiomorpholide) (49)	66
86	3-acetyl-BT	S_8, C_5H_5N, 165°, sealed tube	BT-(3-acetamide) (37)	68
87	5-amino-1	HNO_2, H_3O^+, 0°; then Na_2CO_3, CuCN, KCN, reflux	5-cyano-1 (13)	66
88	5-amino-BT	HNO_2, H_3O^+, 0°; then CuCN, reflux	5-cyano-BT (43)	67
89	5-amino-1	H_2SO_4, $NaNO_2$, 2°; then H_2O, reflux	5-hydroxy-1 (65)	66
90	3-amino-Q	H_2SO_4, $NaNO_2$, 0°; then H_2O, 50°	3-hydroxy-Q	69
91	5-bromo-1	KNH_2, liq. NH_3, ether, -70°	4-amino-1 (42), 5-amino-1 (13)	66
92	3-bromo-Q	KNH_2, liq. NH_3, ether, -33°	3-amino-Q (37), 4-amino-Q (45)	70
93	thieno-pyridone 15	$POCl_3$, reflux	6-chloro-1 (31)	42

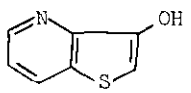
Table 8.2. (continued)

Example No.	Substrate Used	Reagent(s) and Reaction Conditions	Product(s) Formed and Yield (%)	Reference
94	2-quinolone (16)	$POCl_3$, PCl_5, 135°	2-chloro-Q	71
95	4-hydroxy-1 (33)	$POCl_3$, reflux	4-chloro-1 (83)	72
96	4-quinolone (34)	$POCl_3$, PCl_5, 105°	4-chloro-Q	73

It is clear from the examples in Tables 8.1 and 8.2 that the TP system (especially 1) remains intact during a variety of acidic and basic reactions, rearrangements, reductions, and replacements of substituents. There is little information on the stability of the TP system toward oxidative attack on substituents, though 5-acetyl-1 has been converted into the 5-carboxylic acid by means of hypochlorite in aqueous dioxane (haloform reaction).[66]

9. CHARACTERISTICS OF OH AND NH_2 SUBSTITUENTS

The question of tautomerization in hydroxy deriatives of TP has been summarized by Barker,[12] who noted that (in analogy to the isosteric hydroxyquinolines) appropriate structural formulations are given as 31 (3-hydroxy-2),



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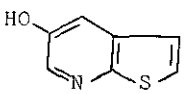

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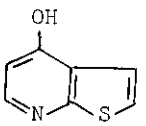

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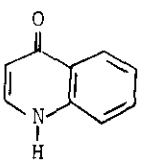

34

32 (5-hydroxy-1), and 15 (thieno[2,3-b]pyrid-6(7H)one). In contrast, however, spectral evidence indicates that 33 exists in the enol form of 4-hydroxy-1,[72] while the isosteric quinoline compound is well documented as the keto form, 4-quinolone (34).[74] Further investigation of the tautomerism of 33 seems desirable.

The reported amino derivates of 1 are the 3-, 4-, and 5-isomers. As with the aminoquinolines,[74] they apparently exist as the amino (rather than imino) tautomers.[15,39,66] The 3-isomer slowly deteriorates in air,[75] so that it has a stability greater than that of 3-amino-BT,[32] but less than that of 5-amino-Q. 4-Amino-1 (pK_a 6.41) is considerably more basic than the 5-isomer (pK_a 3.43), in analogy with the isosteric 4-amino-Q (pK_a 9.17) and 3-amino-Q (pK_a 4.95) isomers.[14] Considerable difference has been noted in the ease with which 4- and 5-amino-1 form Schiff's bases.[39,66]

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