Methods for Preparing Benzimidazo[2,1-*b*]quinazolin-12-ones and Related Compounds

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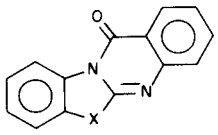
Until recently, the only representatives of heterocyclic system **1** reported were benzothiazo[2,1-*b*]quinazolin-12-(6*H*)-one (**1**, X = S) (1) and its benzimidazole analog (**1**, X = NH) (2). This year Kaushal and his coworkers reported



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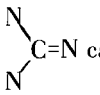
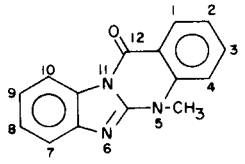
the synthesis of a number of benzothiazoquinazolinones (3).

We were in need of a range of derivatives of these tetracyclic systems, particularly the benzimidazo series, and since some of the required compounds could not be prepared by the established procedures we developed some new ones. A small difference in the nature of the aromatic substitution of the required tetracyclic compound often demanded that a different preparative procedure be used. It may well prove that some of these findings may find application in other similar heterocyclic systems. For example, the use of anthraniloyl chloride amine hydrochlorides as acylating agents represents a novel means of protecting the amine group prior to reaction.

The position of the double bond at the  carbon in the benzimidazoquinazolones, in which it could be at N-5 or N-6, has yet to be ascertained. It has been assumed to be at N-6 and we have verified this. 5-Methylbenzimidazo[2,1-*b*]quinazolin-12(6*H*)-one (**2**) was synthesized using methyl *N*-methyl anthranilate and 2-chlorobenzimidazole; and the 6-methyl isomer **3** by the action of dimethyl sulfate on **1** (X = NH). In **2** the position of the double bond under consideration is predetermined to between 5a and 6. As can be seen in Figure 1, the ultraviolet spectra of **1** (X = S) and **3** are quite similar, while that of **2** is rather different.

The infrared spectra of the *N*-substituted compounds provided a further means of assigning the position of the  double bond. The carbonyl absorption of **2** occurs at 1724 cm^{-1}, while that of **3** is at 1684 cm^{-1}. All the *N*-alkyl derivatives mentioned below absorb at 1700-1678 cm^{-1}, and the spectra of the *N*-acyl and *N*-aroyl compounds exhibit this peak of 1702-1690 cm^{-1} and 1698-1682 cm^{-1} respectively. This is strongly indicative of substitution at *N*-6 as opposed to *N*-5.



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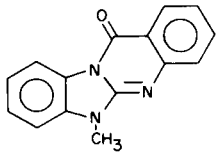

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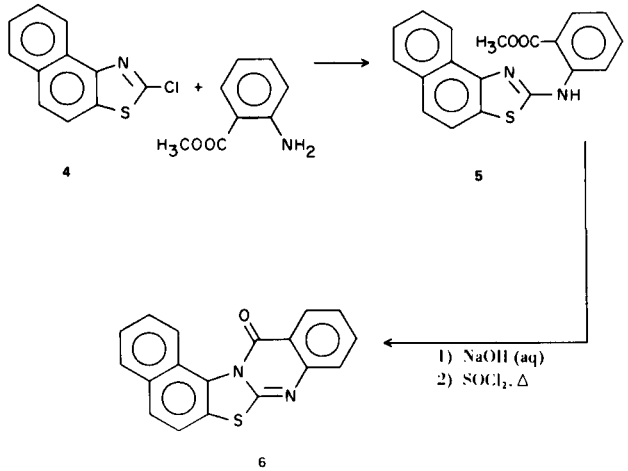
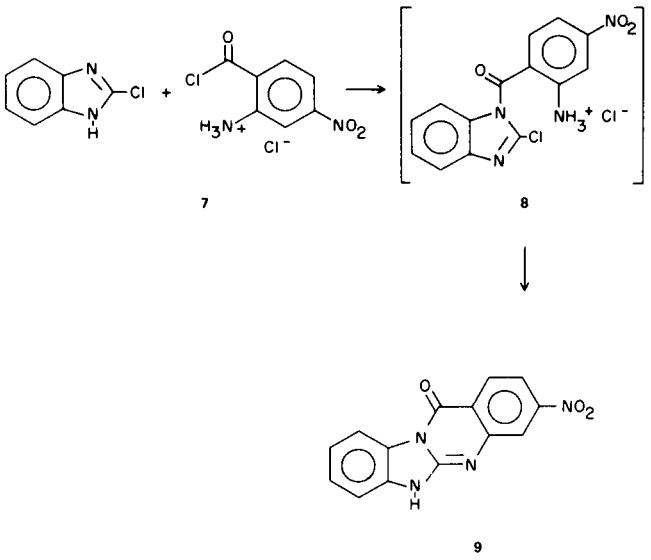
A method which proved to have some generality involved heating together the appropriately substituted 2-aminobenzimidazole and anthranilic acid derivative with trifluoroacetic acid as a catalyst. (Without the trifluoroacetic acid, using the conditions of Antaki and Petrow (4) for preparing tetrahydrobenzimidazoquinazolones, gross mixtures were obtained from which no desired tetracyclic products were isolated).



4 **5** **6**

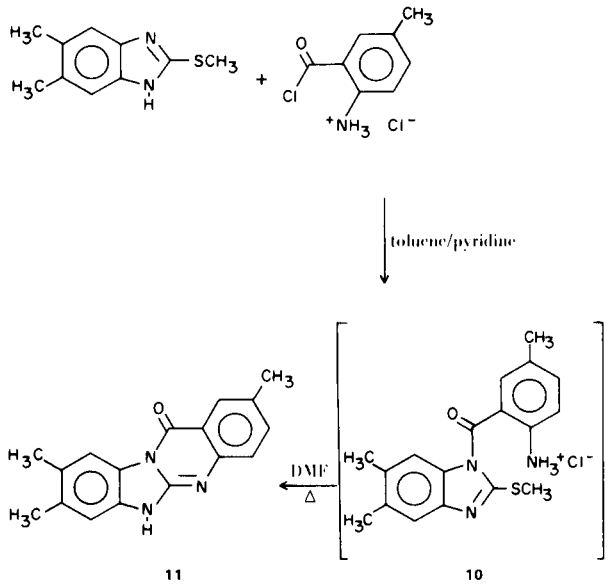
Heating 2-chloronaphtho[1,2-*d*]thiazole (4) with methyl anthranilate gave the methyl ester **5**. This would not cyclize even under the most rigorous conditions, presumably due to steric hindrance. However, the carboxylic acid obtained by hydrolysis of the ester underwent facile cyclization to **6** (presumably *via* the intermediate acid chloride) on refluxing in thionyl chloride.

A similar procedure succeeded with 2-chlorobenzimidazole and 2-amino-4-nitrobenzoic acid, which would not react directly. The anthranilic acid derivative was converted to its hydrochloride, which on refluxing in thionyl chloride afforded the acid chloride amine hydrochloride **7**. This compound, without prior purification, provided the 3-nitro tetracyclic **9** on heating with 2-chlorobenzimidazole in benzene, acylation to give **8** being the assumed first step.



The reported (5) conversion of 5,6-dimethylbenzimidazole-2-one to the 2-chloro compound, using phosphorus oxychloride, did not, in our hands, provide any practical yields of the 2-chloro derivative.

The trimethyl tetracyclic product **11** not obtainable by previously described techniques, was made by a procedure involving rather specific conditions. The appropriate methyl anthraniloyl chloride hydrochloride in pyridine was added to 2-methylmercapto-5,6-dimethylbenzimidazole in toluene and the mixture was stirred for two hours at room temperature. Dimethylformamide was then added to the mixture which was heated to give the required trimethyltetracyclic derivative **11**.

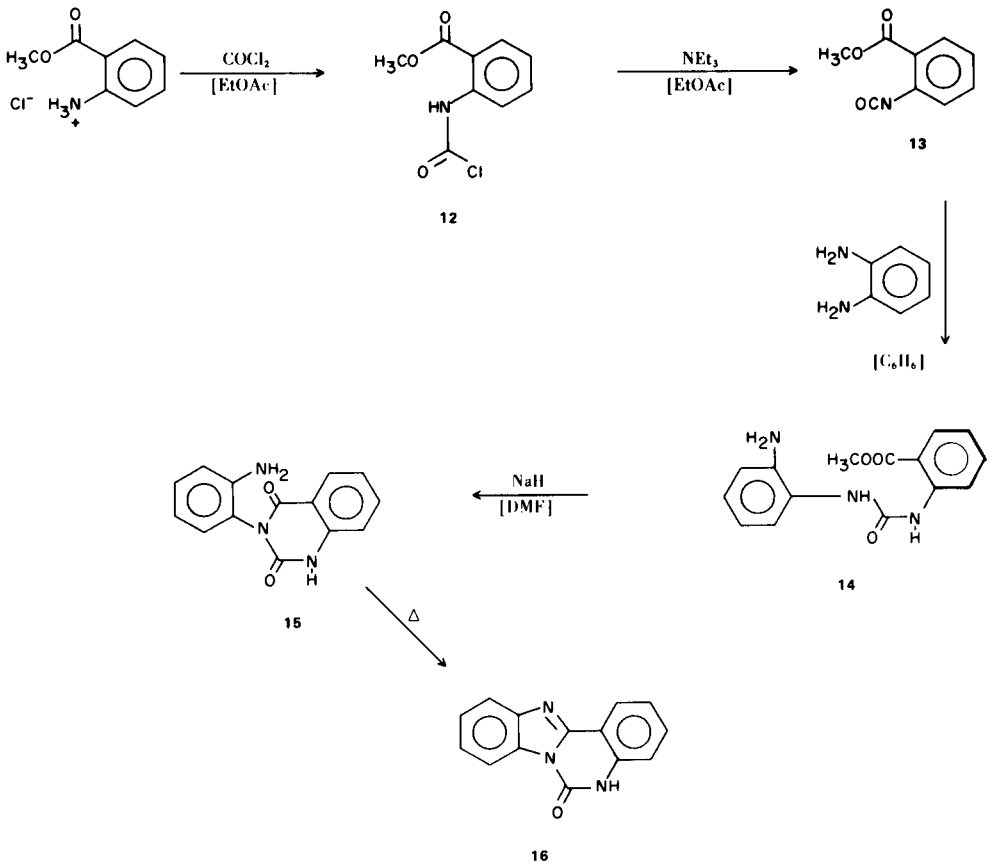


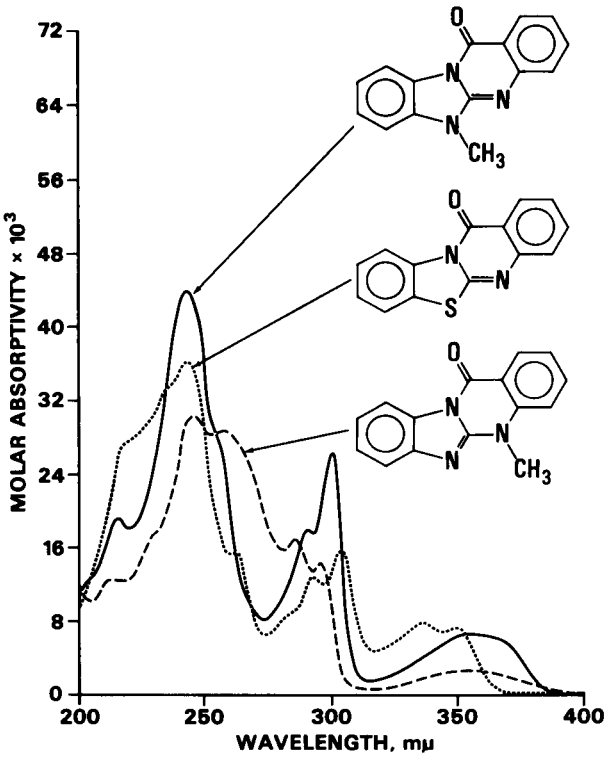
Treatment of 2-mercapto-5,6-dimethylbenzimidazole with chlorine gave 2,4,7-trichloro-5,6-dimethylbenzimidazole (6). This trichlorobenzimidazole readily formed 7,10-dichlorotetracyclic products.

In another approach, using methyl anthranilate as a model, its hydrochloride was converted to the carbamoyl chloride **12**, which was quite stable at room temperature; heat was required to transform it to the isocyanate **13**. Treatment of **12** with triethylamine rapidly afforded good yields of the isocyanate **13**, which reacted with *o*-phenylene diamine to give urea **14**. The action of sodium hydride in dimethylformamide on this urea resulted in dehydration to **15**, which on heating provided **16** (7) rather than the required benzimidazo[2,1-*b*]quinazolin-12(6*H*)-one.

Alkylation and acylation of the benzimidazo[2,1-*b*]-quinazolin-12(6*H*)-ones has not been previously described. Such functionalization was facile, the *N*-6 derivative usually predominating. The 6-methyl and ethyl analogs were prepared by reaction with the corresponding dialkyl sulfate. In the methylation a gross mixture of 6- and 5-methyl compounds (inseparable by crystallization or chromatography) resulted. On protracted treatment with dimethyl sulfate, the *N*-5 methyl derivative underwent quaternization much more rapidly than its *N*-6 isomer; and the water solubility of the quaternary compound provided for its separation from the 6-substituted compound.

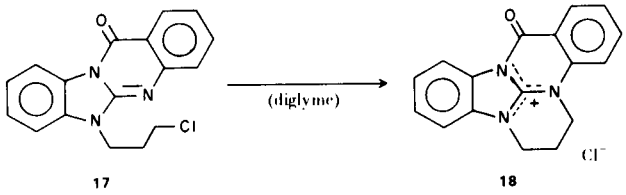
A number of 6-alkyl and 6-acyl compounds were prepared. Except for the above and the *o*-acetylbenzoyl derivative (which was obtained by reaction of *o*-acetylbenzoyl chloride with **1**, X = NH, in pyridine) these were synthesized by converting the tetracyclic compound to its sodium salt, using sodium hydride in dimethylformamide, and then treating this with the appropriate halogen compound.





Attempts to obtain *N*(6)-mesitoyl derivatives by this procedure failed. However, if the sodium salt was prepared and reacted with the acid chloride in tetrahydrofuran, good yields of the mesitoyl products were produced (8). The *N*(6)-adamant-1-oyl and -pivaloyl compounds could not be prepared under a variety of conditions.

The chloropropyl derivative **17**, prepared in the usual manner, underwent cyclization to the ionic species **18** on being refluxed in diglyme.



EXPERIMENTAL

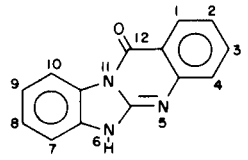
5-Methylbenzimidazo[2,1-*b*]quinazolin-12(5*H*)-one (**2**).

A suspension of 2-chlorobenzimidazole (3.2 g.) in methyl *N*-methylanthranilate (3.63 g.) was heated at 150-155° for 15 minutes. The solid dissolved; vigorous gas evolution was observed; then solidification occurred. After cooling, the crude product was

TABLE I

Benzimidazo[2,1-*b*]quinazoline-12-ones not described in the text

X =



No.	Compound	Mp °C	Molecular Formula	% Yield	Analysis (a) C	H	N	Cl	I
1	6-Ethyl-	230-232	$C_{16}H_{13}N_3O$	27	72.98 72.89	4.98 4.73	15.96 15.98		
2	6-Isopropyl-	186-188	$C_{17}H_{15}N_3O$	42	73.63 73.77	5.45 5.54	15.15 15.15		
3	6-*n*-Octyl-	103-104	$C_{22}H_{25}N_3O$	22	76.05 76.28	7.25 7.51	12.10 12.38		
4	6-Benzyl-	218-220	$C_{21}H_{15}N_3O$	38	77.52 77.34	4.65 4.74	12.92 12.74		
5	6-Methoxymethyl-	221-223	$C_{16}H_{13}N_3O_2$	73	68.80 68.74	4.69 4.92	15.05 15.17		
6	6-(3-Dimethylamino-*n*-propyl)-	164-165	$C_{19}H_{20}N_4O$	17	71.22 71.26	6.29 6.40	17.49 17.59		
7	6-Benzoyl-	225-227	$C_{21}H_{13}N_3O_2$	67	74.32 74.06	3.86 4.03	12.38 12.55		
8	6-(2,4-Dimethylbenzoyl)-	213-214	$C_{23}H_{17}N_3O_2$	43	75.19 75.05	4.66 4.66	11.44 11.36		
9	6-(3,5-Dimethylbenzoyl)-	259-260	$C_{23}H_{17}N_3O_2$	37	75.19 75.15	4.66 4.76	11.44 11.16		
10	6-(2-Chlorobenzoyl)-	223-225	$C_{21}H_{12}N_3O_2Cl$	60	67.47 67.40	3.23 3.49	11.24 10.97	9.48 9.78	
11	6-(2,4-Dichlorobenzoyl)-	202-203	$C_{21}H_{12}N_3O_2Cl$	40	61.78 61.87	2.71 2.58	10.29 10.41	17.37 17.54	
12	6-Phenacyl-	200-201	$C_{22}H_{15}N_3O_2$	64	74.77 74.91	4.28 4.50	11.89 12.12		
13	6-Phenylcyclohexylacetyl-	227-229	$C_{28}H_{25}N_3O_2$	54	77.22 77.47	5.79 6.09	9.65 9.90		
14	6-Palmitoyl-	216-219	$C_{30}H_{39}N_3O_2$	53	76.07 75.84	8.30 8.11	8.87 9.03		
15	6-(2-Norbornen-5-ylcarbomyl)-	215-218	$C_{22}H_{17}N_3O_2$	59	74.35 74.24	4.82 4.92	11.84 12.04		
16	6-(2-Carboethoxymethyl)-	244-245	$C_{18}H_{15}N_3O_3$	68	67.28 67.39	4.71 5.46	13.08 12.74		
17	6-(4-Carbomethoxy-*n*-butyl)-	130-132	$C_{20}H_{19}N_3O_3$	62	68.75 68.70	5.48 5.85	12.03 12.36		
18	6-(3-Carbomethoxypropionyl)-	190-191	$C_{19}H_{15}N_3O_4$	59	65.32 65.06	4.33 4.27	12.03 12.30		
19	6-(4-Carbomethoxybutyryl)-	159-161	$C_{20}H_{17}N_3O_4$	47	66.11 66.06	4.72 4.85	11.57 11.90		
20	6-(4-Carbomethoxypropionyl)-methyl	199-201	$C_{20}H_{17}N_3O_4$	18	66.11 65.98	4.72 4.87	11.57 11.56		

TABLE I (Continued)

21	3-Methyl-	328-335	$C_{15}H_{11}N_3O$	48	72.27 72.03	4.45 4.60	16.86 16.80	
22	2-Iodo-	272 (d)	$C_{14}H_8N_3OI$	7	46.56 46.83	2.23 2.38	11.64 11.57	35.14 35.05
23	3,8,9-Trimethyl-	337 (d)	$C_{17}H_{15}N_3O$	4	73.63 73.42	5.45 5.63	15.15 14.95	
24	3,8,9-Trimethyl-6-acetyl-	267-268	$C_{19}H_{17}N_3O_2$	74	71.45 71.46	5.37 5.52	13.16 13.38	
25	2,8,9-Trimethyl-6-(2,4-dimethylbenzoyl)-	258-260	$C_{26}H_{23}N_3O_2$	30	76.26 76.07	5.66 5.78	10.26 10.12	
26	2,8,9-Trimethyl-6-(2,4,6-trimethylbenzoyl)-	263-265	$C_{27}H_{25}N_3O_2$	66	76.57 76.49	5.95 6.05	9.92 10.04	

(a) Top numbers are analyses calculated, bottom are analyses found.

recrystallized from diglyme to give pure **2** (2.17 g.), m.p. 273-275°.

Anal. Calcd. for $C_{15}H_{11}N_3O$: C, 72.27; H, 4.45; N, 16.86. Found: C, 72.31; H, 4.55; N, 16.78.

6-Methylbenzimidazo[2,1-*b*]quinazolin-12(6*H*)-one (**3**).

The unsubstituted parent tetracycle **1** (X = NH) (1.18 g.) was suspended in dry DMF (50 ml.); the mixture was stirred at 120° while methyl sulfate (2 ml.) in DMF (25 ml.) was added dropwise. Following this addition, the mixture was heated at this temperature for 3 hours. Pyridine (1.0 ml.) was then added, and the mixture was heated at reflux for 55 hours. On cooling to room temperature, the product separated as crystals which were collected by filtration. A single recrystallization provided pure **3** (0.43 g.), m.p. 273-274°.

Anal. Calcd. for $C_{15}H_{11}N_3O$: C, 72.27; H, 4.45; N, 16.86. Found: C, 72.23; H, 4.63; N, 16.74.

Note: Tlc showed that if refluxing was continued for less than 55 hours, traces of **2** remained in the mixture.

8,9-Dimethylbenzimidazo[2,1-*b*]quinazolin-12(6*H*)-one.

A mixture of 2-amino-5,6-dimethylbenzimidazole (3.22 g.), methyl anthranilate (3.9 ml.), and trifluoroacetic acid (1.48 ml.) were stirred under reflux in an oil bath at 225-230° for 6 hours. The cooled mixture was suspended in chloroform; the suspension was washed with water and filtered to give the crude dimethyl tetracycle, which was purified (0.47 g.), m.p. 324-330° dec., by a single crystallization from aqueous DMF.

Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 72.98; H, 4.98; N, 15.96. Found: C, 72.96; H, 5.22; N, 15.68.

13*H*-Naphtho[1,2-*d*]thiazolo[2,3-*b*]quinazolin-13-one (**6**).

2-Chloronaphtho[1,2-*d*]thiazole (10.0 g.) and methyl anthranilate (7.5 g.) were heated with stirring in diglyme (175 ml.) under reflux for 15 hours, cooled, and poured into ice water. Filtration gave a crude product which was air dried and recrystallized twice from hexane to afford 5 (3.97 g.), m.p. 142-144°.

Anal. Calcd. for $C_{19}H_{14}N_2O_2S$: C, 68.25; H, 4.22; N, 8.38; S, 9.59. Found: C, 67.99; H, 4.38; N, 8.38; S, 9.79.

A mixture of the above ester (1.80 g.), sodium hydroxide (5 g.), ethanol (50 ml.), and water (15 ml.) was refluxed for 6 hours, cooled, acidified to *p*H 2 with concentrated hydrochloric acid and filtered. One recrystallization of the product from ethanol gave the pure acid (0.85 g.), m.p. 243-244°.

Anal. Calcd. for $C_{18}H_{12}N_2O_2S$: C, 67.44; H, 3.77; N, 8.74; S, 10.00. Found: C, 67.69; H, 4.00; N, 8.70; S, 10.25.

The acid (0.5 g.), pyridine (0.25 ml.), and thionyl chloride (0.4 ml.) were refluxed with stirring for 1 hour. After evaporation to dryness under reduced pressure, the resulting solid was slurried with water, collected by filtration, and air-dried. Pure pentacyclic **6** (0.25 g.), m.p. 193-195°, was afforded on recrystallization from benzene.

Anal. Calcd. for $C_{18}H_{10}N_2OS$: C, 71.49; H, 3.33; N, 9.26; S, 10.60. Found: C, 71.26; H, 3.36; N, 9.42; S, 10.69.

3-Nitrobenzimidazo[2,1-*b*]quinazolin-12(6*H*)-one (**9**).

Concentrated hydrochloric acid was added to a stirred slurry of 4-nitroanthranilic acid (5.46 g.) in water (100 ml.) until complete solution was achieved. This solution was evaporated to dryness under reduced pressure. The residue was suspended in thionyl chloride (72 ml.), and the suspension was refluxed with stirring for 1.5 hours. The resulting mixture was evaporated to dryness under reduced pressure. Dry benzene (50 ml.) was added and then removed under reduced pressure twice to remove the last traces of thionyl chloride.

A mixture of the above crude acid chloride hydrochloride and 2-chlorobenzimidazole (4.58 g.) in dry benzene (150 ml.) was refluxed with stirring for 5 hours. After refrigeration for 48 hours, the product was collected by filtration and recrystallized from aqueous DMF to give pure **9** (1.39 g.), m.p. 400° dec.

Anal. Calcd. for $C_{14}H_8N_4O_3$: C, 60.00; H, 2.88; N, 19.99. Found: C, 59.76; H, 3.01; N, 20.09.

2,8,9-Trimethylbenzimidazo[2,1-*b*]quinazolin-12(6*H*)-one (**11**).

Concentrated hydrochloric acid (50 ml.) was added to a mixture of 2-amino-5-methylbenzoic acid (50 g.) in water (400 ml.), and the resulting solution was evaporated to dryness under reduced pressure. The dry amine salt was converted to 2-amino-5-methylbenzoyl chloride hydrochloride in the manner described above, and the crude product was suspended in dry toluene (100 ml.). This suspension was stirred magnetically while being added to a stirred solution of 2-methylmercapto-4,5-dimethylbenzimidazole (42.5 g.) in pyridine (128 ml.). Two hours later, when tlc indicated complete reaction, dry DMF (720 ml.) was added. While the mixture was refluxed with stirring for 5 hours, a solid was deposited. The slurry was refrigerated for 12 hours and then filtered; the product was washed with cold DMF to provide, after drying, pure trimethyltetracyclic **11** (24.8 g.), m.p. >411° dec.

Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.38; H, 5.71; N, 15.18.

Benzimidazo[1,2-*c*]quinazolin-6(5*H*)-one (**16**).

A solution of methyl anthranilate (6.5 g.) in benzene (200 ml.) was stirred while being saturated with hydrogen chloride gas. The solution was left sealed for 12 hours with stirring. The white solid which precipitated was collected by filtration and suspended with stirring in ice-cold ethyl acetate (700 ml.), previously saturated with phosgene. The stirred mixture was maintained at ice-bath temperature, and phosgene was passed over the surface until complete solution of the solid occurred. The solvent was then removed under reduced pressure to give a residue of white crystalline needles. The nmr [3.97 (3H), OCH_3; 6.9-8.4 (4H), aromatic; 10.3 (1H), NH; ppm)] and ir spectral characteristics of this crude product were consistent with its being carbamoyl chloride **12**.

The above needles were dissolved in dry benzene (50 ml.), and triethylamine (5.0 g.) was added dropwise with stirring. The resulting suspension was filtered, the ir spectrum of the filtrate exhibited a strong isocyanate peak (2268 cm^{-1}). This filtrate was added slowly to a stirred solution of *o*-phenylene diamine (6.5 g.) in dry benzene (600 ml.), whereupon a heavy precipitate was deposited. This product was collected by filtration, washed with benzene, and dried, affording pure **14** (8.6 g.), m.p. 153-155°.

Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.98; H, 5.45; N, 14.46.

The urea **14** (4.28 g.) was dissolved in dry DMF (50 ml.); sodium hydride (0.6 g., 60% suspension in mineral oil) was added; and the mixture was stirred for 3 hours by which time hydrogen evolution had ceased.

To an aliquot (5 ml.) of the resulting solution was added ammonium chloride (100 mg.); the mixture was concentrated under reduced pressure, then diluted with water. The precipitate formed was collected by filtration and recrystallized from acetonitrile-benzene to give **15** (0.22 g.), m.p. 282-284°.

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.39; H, 4.38; N, 16.59. Found: C, 66.56; H, 4.47; N, 16.3.

The remainder of the above sodium hydride-treated solution (45 ml.) was refluxed for 20 hours, cooled, poured into ice water; and the precipitate was collected by filtration. Recrystallization from DMF provided pure **16** (0.97 g.), m.p. 341-342°. Infrared spectrum identical with a sample kindly provided by Dr. Taylor (7).

Anal. Calcd. for $C_{14}H_9N_3O$: C, 71.48; H, 3.86; N, 17.86. Found: C, 71.65; H, 4.10; H, 17.93.

6-(2-Acetoxybenzoyl)benzimidazo[2,1-*b*]quinazolin-12(6*H*)-one.

The unsubstituted parent tetracyclic compound **1** (X = NH) (4.0 g.) was stirred in dry DMF (60 ml.) containing anhydrous pyridine (3 ml.) while acetyl salicyloyl chloride (4.4 g.) was added in dropwise fashion. The slurry became thinner in consistency; after 7 hours when tlc indicated the reaction to be complete, it was poured into ice water with stirring. Filtration provided a light-yellow solid which was air-dried and recrystallized from DMF to give pure product (3.0 g.), m.p. 202-203°.

Anal. Calcd. for $C_{23}H_{15}N_3O_4$: C, 69.51; H, 3.81; N, 10.59. Found: C, 69.21; H, 4.10; N, 10.41.

6-(*n*-Amyl)benzimidazo[2,1-*b*]quinazolin-12(6*H*)-one.

The unsubstituted parent tetracycle (2.35 g.) was stirred in dry DMF (70 ml.) with sodium hydride (0.53 g., 57% dispersion in mineral oil) until complete solution had occurred. *n*-Amyl bromide (3.1 g.) was added; the mixture was stirred for 16 hours by which time the yellow color of the anion had disappeared. The resulting suspension was poured into ice water with stirring, and the product was collected by filtration. After air drying, two recrystallizations from benzene provided pure *n*-pentyl tetracycle (1.71 g.), m.p. 177-178°.

Anal. Calcd. for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found: C, 74.78; H, 6.35; N, 13.82.

6-(2,4,6-Trimethylbenzoyl)benzimidazo[2,1-*b*]quinazolin-12(6*H*)-one.

The parent unsubstituted tetracycle (7.1 g.) was stirred in dry THF (200 ml.) with sodium hydride (1.61 g., 57% dispersion in mineral oil) until completely dissolved. Mesitoyl chloride (6.6 g.) was added; the mixture was stirred for 16 hours, when the yellow color had disappeared. The mixture was poured into ice water with stirring and filtered; and the crude product was air-dried. Two recrystallizations from acetonitrile gave pure material (6.3 g.), m.p. 200-202°.

Anal. Calcd. for $C_{24}H_{19}N_3O_2$: C, 75.57; H, 5.02; N, 11.02. Found: C, 75.41; H, 4.79; N, 11.22.

2,3-Dihydro-8-oxo-1*H*,8*H*-3a,7b,12b-triazabenz[*e*]acyphenanthrylen-12c-iminium Chloride (**18**).

Crude chloropropyl compound **17** (10 g.), prepared from 3-chloropropyltosylate, was suspended in dry diglyme (100 ml.); the mixture was refluxed with stirring for 30 minutes. Initially, complete solution occurred; then a white solid was deposited. After cooling, the product was collected by filtration and recrystallized from methanol-2-propanol to give pure **20** (5.74 g.), m.p. 142-144°.

Anal. Calcd. for $C_{17}H_{14}N_3OCl$: C, 65.49; H, 4.53; N, 13.48; Cl, 11.37. Found: C, 65.57; H, 4.31; N, 13.36; Cl, 11.45.

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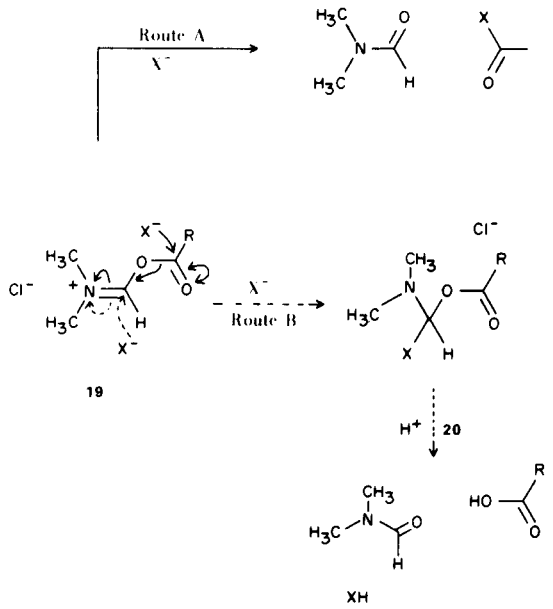
(8) It is known that the acyl halides react with dimethylformamide to give an ionic species (9) and we suggest these may be structure **19**. In the usual course, nucleophilic attack at the car-

bonyl group leads to the acyl derivative (Route A). On the other hand, when R is a bulky group (as with mesitoyl chloride), nucleophilic attack at the enamine carbon is preferred (Route B). This would give the intermediate **20**, which would decompose to the parent tetracycle and the carboxylic acid on aqueous processing.



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