Preparation of Imidazo[2,1-b]quinazolin-5(3H)-ones and Related Tricyclic Systems Using a Novel, Double Displacement Reaction

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New methodology is described for the construction of tricyclic heterocycles. Thus, a double displacement reaction of 1-(2-fluorobenzoyl)-2-methylthio-2-imidazoline (**8a**) with 1,1-dialkylhydrazines gave 10-substituted 2,10-dihydroimidazo[2,1-b]quinazolin-5(3H)-ones in good yield. The corresponding 1-(2-nitrobenzoyl)-2-methylthio-2-imidazolines also underwent double displacement reactions with hydrazines. Other tricyclics made using double displacement reactions were pyrimido[2,1-b]quinazolines, imidazo[1,2-a]pyrido[2,3-d]pyrimidines, and imidazo[1,2-a]pyrazolo[3,4-d]pyrimidines. Treatment of **8a** with hydrazine hydrate or methylhydrazine gave products resulting from displacement, but did not afford fused benzotriazepinones.

We recently required a synthesis for imidazo[2,1-b]quinazolin-5(3H)-ones **1** and related tricyclic systems in which the center, pyrimidinone ring contained an *N*-amino substituent on the available nitrogen atom. We wished to evaluate these compounds as potentially selective trachael smooth muscle relaxants. The imidazo[2,1-b]quinazolin-5(3H)-one ring system is known, and the parent compound and 10-alkyl and 10-aryl substituted versions have been prepared, starting from *N*-alkyl and *N*-arylisatoic anhydrides, respectively [1,2].

In a retrosynthetic sense, we envisioned an expedient sequence in which compounds of general structure **2**, where X and Y represent leaving groups, might undergo double displacement reactions with appropriately substituted hydrazines **3** to provide imidazoquinazolinones **1** directly. Although displacement reactions have been employed to create the middle ring of tricyclic systems sequentially [3] or in one step [1,2,4], we were unaware of a synthon like **2** which was designed for double displacement [8,12]. This report describes the synthesis of synthons **2** (and related synthons) and their utility in the preparation of imidazo[2,1-b]quinazolin-5(3H)-ones **1** and related tricyclic systems *via* novel double displacement reactions.
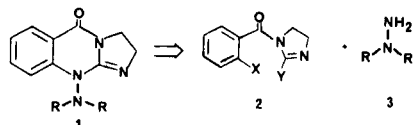
As an initial approach to a synthon, we envisioned a monoacylation of ethylenethiourea (**5**) with an *ortho*-X-substituted benzoyl chloride, followed by *S*-alkylation to introduce an alkylthio Y-group. This approach has been used previously in the preparation of compounds related to **2** [13,14]. Indeed, we found that ethylenethiourea (**5**) produced monobenzoylated derivatives **6a** and **b** when treated with benzoyl chloride (**4a**) and 2-fluorobenzoyl chloride (**4b**), respectively (Scheme I). However, the major products of these acylations were the undesired diacylated species **7a** and **b**, even when the benzoyl chloride was added to excess **5**. Although the mono- and diacylated compounds could be separated by fractional crystallization, the process was tedious and would have detracted from the utility of a synthon. Thus, we decided to use an *S*-alkylated version of **5** in which the leaving group Y was already in position and which would allow only one site for acylation. Treatment of 2-fluorobenzoyl chloride (**4b**) with 2-methylthio-2-imidazoline hydroiodide and pyridine in methylene chloride cleanly gave synthon **8a**.

Scheme I

4a, R'= H
b, R'= F

5

6a, R'= H
b, R'= F

7a, R'= H
b, R'= F

8a, R'= F
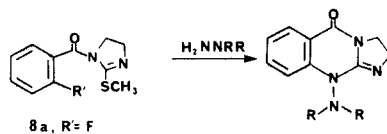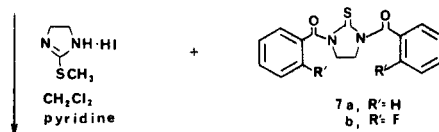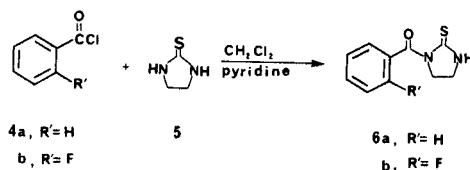
9a, NRR = 4-morpholinyl
b, NRR = 1-piperidinyl
c, NRR = 1-homopiperidinyl
d, NRR = dimethylamino
e, NRR = benzyl

Treatment of **8a** with hydrazines gave the 10-substituted imidazo[2,1-b]quinazolinones **9a-e** in good yields (71-80%) as shown in Scheme I. Thus, the concept of creating our desired tricyclic system in one step *via* a double displacement process was demonstrated. Compounds **9a**,

9c, and 9e were prepared by brief treatment of 8 with the neat hydrazines at reflux. Under these same conditions with 1-aminopiperidine and 1,1-dimethylhydrazine, in attempts to prepare compounds 9b and 9d, 8a was recovered in 73% and 99% yields, respectively. Since the minimum temperature required for the double displacement reaction was apparently *ca.* 160°, 2-methoxyethyl ether (diglyme), bp 162°, was employed as a cosolvent for the preparation of 9b. For the preparation of 9d, 8a was heated with excess 1,1-dimethylhydrazine in a sealed glass tube at 165° for 3 hours.

The extension of this methodology to synthons where the leaving group on the benzoyl portion of the molecule was nitro is shown in Scheme II. This extension was important, since 2-nitrobenzoyl chlorides are more accessible than 2-fluorobenzoyl chlorides, and it allowed us to prepare compounds necessary for structure-activity comparison. Thus, we were able to prepare imidazoquinazolines in which the aminoguanidine portion of the molecule (which we felt was important for biological activity) was affected by *para* substituents which were electron-donating (methyl) and electron-withdrawing (chloro).

Also shown in Scheme II is the use of double displacement methodology for the synthesis of pyrimido[2,1-*b*]quinazolin-6-ones 12. 3,4,5,6-Tetrahydro-2-pyrimidinethiol was *S*-methylated to give hydroiodide salt 10 [15]. Acylation of 10 with benzoyl chlorides 4 gave benzamides 11, which were then treated with hydrazines, either neat or in diglyme, to give pyrimido[2,1-*b*]quinazolin-6-ones 12.
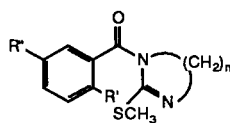
Scheme II
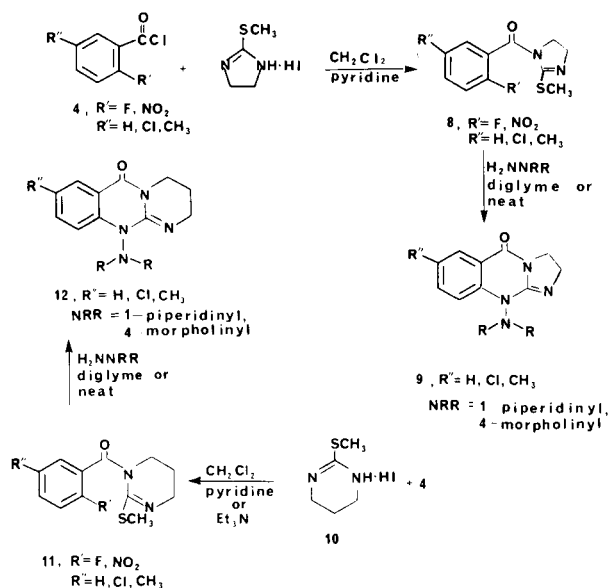
Physical constants for the 1-benzoyl-4,5-dihydro-2-methylthio-1*H*-imidazoles 8 and 1-benzoyl-1,4,5,6-tetrahydropyrimidines 11 are compiled in Table I. Yields for these acylation products were uniformly good (88-99%). Table II lists physical constants and preparation conditions for the products of the double displacement reactions, namely, the imidazo[2,1-*b*]quinazolin-5(3*H*)-ones 9 and the 6*H*-pyrimido[2,1-*b*]quinazolin-6-ones 12. Yields for the imidazoquinazolinones 9, with some exceptions, were quite good.

Table I

Physical Constants for 1-Benzoyl-4,5-dihydro-2-methylthio-1*H*-imidazoles 8 and 1-Benzoyl-2-methylthio-1,4,5,6-tetrahydropyrimidines 11

Compound No.	R′	R″	n	mp °C (Recrystallization solvent)	% yield	Base	Molecular Formula	*Anal.* Calcd.			Found		
								C	H	N	C	H	N
8a	F	H	2	100-102 (toluene/hexane)	89	pyridine	$C_{11}H_{11}FN_2OS$	55.44	4.65	11.76	55.40	4.66	11.75
8b	NO₂	Cl	2	135-136 (MeOH)	99	pyridine	$C_{11}H_{10}ClN_3O_3S$	44.08	3.36	14.02	43.82	3.27	14.04
8c	NO₂	CH₃	2	125-126 (EtOH/H₂O)	98	Et₃N	$C_{12}H_{13}N_3O_3S$	51.60	4.69	15.04	51.52	4.64	14.90
11a	F	H	3	oil	91	Et₃N	$C_{12}H_{13}FN_2OS$	57.12	5.19	11.10	57.09	5.22	11.04
11b	NO₂	Cl	3	112-113 (DMF/H₂O)	92	Et₃N [1]	$C_{12}H_{12}ClN_3O_3S$	45.94	3.86	13.39	45.82	3.77	13.41
11c	NO₂	CH₃	3	145-147	88	Et₃N	$C_{13}H_{15}N_3O_3S$	53.23	5.15	14.32	53.37	5.23	14.25

[1] When pyridine was used as the base, a product mixture resulted which was separated by flash chromatography. In addition to 11b, which was isolated in only 15% yield, mono- and diacylated derivatives of 1,3,4,5,6-pentahydropyrimidin-2-one were obtained.

Table II

Physical Constants for Imidazo[2,1-*b*]quinazolin-5(3*H*)-ones **9** and 6*H*-Pyrimido[2,1-*b*]quinazolin-6-ones **12**
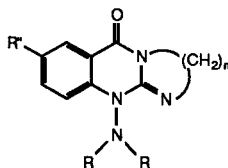
Compound No.	NRR	R''	n	mp °C (Recrystallization solvent)	% yield	Solvent (reaction time)	Molecular Formula	*Anal.* Calcd.			Found		
								C	H	N	C	H	N
9a	4-morpholinyl	H	2	250-251 (DMF/H$_2$O)	74	neat (10 min)	C$_{14}$H$_{16}$N$_4$O$_2$	61.75	5.92	20.58	61.68	5.99	20.76
9b	1-piperidinyl	H	2	229-230 (MeOH)	71	diglyme (15 hours)	C$_{15}$H$_{18}$N$_4$O	66.66	6.71	20.73	66.39	6.80	20.87
9c	1-homopiperidinyl	H	2	206-208 (DMF/H$_2$O)	76	neat (10 minutes)	C$_{16}$H$_{20}$N$_4$O	67.58	7.09	19.71	67.60	7.12	19.81
9d	dimethylamino	H	2	197-198 (EtOH)	80	diglyme [1] (3 hours)	C$_{12}$H$_{14}$N$_4$O	62.59	6.13	24.33	62.32	6.15	24.20
9e	benzyl	H	2	203-204 [2,3]	71	neat (10 minutes)	C$_{17}$H$_{15}$N$_3$O	73.63	5.45	15.15	73.54	5.53	14.99
9f	4-morpholinyl	Cl	2	238-239 (DMF)	52	neat (15 minutes)	C$_{14}$H$_{15}$ClN$_4$O$_2$	54.82	4.93	18.27	54.72	4.90	18.52
9g	1-piperidinyl	Cl	2	192-193 [4]	16	diglyme (17 hours)	C$_{15}$H$_{17}$ClN$_4$O	59.11	5.62	18.38	58.94	5.58	18.49
9h	4-morpholinyl	CH$_3$	2	227-228 (EtOH)	44	neat (30 minutes)	C$_{15}$H$_{18}$N$_4$O$_2$	62.75	6.27	19.49	62.90	6.17	19.47
9i	1-piperidinyl	CH$_3$	2	197-199 (EtOH)	16	diglyme (16 hours)	C$_{16}$H$_{20}$N$_4$O	67.58	7.09	19.70	67.19	6.88	19.31
12a	4-morpholinyl	H	3	168-169 (EtOH)	76	neat (20 minutes)	C$_{15}$H$_{18}$N$_4$O$_2$	62.92	6.34	19.57	62.89	6.39	19.41
12b	1-piperidinyl	H	3	177-178 (EtOH/H$_2$O)	40	diglyme (16 hours)	C$_{16}$H$_{20}$N$_4$O	67.58	7.09	19.70	67.25	7.06	19.76
12c	4-morpholinyl	Cl	3	185-187 (EtOH/H$_2$O)	35	neat (20 minutes)	C$_{15}$H$_{17}$ClN$_4$O$_2$	55.99	5.33	17.46	56.06	5.34	17.15
12d	1-piperidinyl	Cl	3	165-167 (EtOH)	8	diglyme (2.5 hours)	C$_{16}$H$_{19}$ClN$_4$O	60.09	5.99	17.52	60.34	6.05	17.82
12e	4-morpholinyl	CH$_3$	3	199-200 (EtOH)	5	neat (30 minutes)	C$_{16}$H$_{20}$N$_4$O$_2$	63.98	6.71	18.65	63.69	6.73	18.63
12f	1-piperidinyl	CH$_3$	3	143-144 (EtOH)	5	diglyme (3 hours)	C$_{17}$H$_{22}$N$_4$O	68.43	7.43	18.78	68.08	7.41	18.61

[1] This reaction was performed in a sealed tube at 165°.   [2] Lit [1] mp 203-205°.   [3] Crystallized directly from reaction medium by the addition of ether, and followed by a water wash.   [4] Crystallized directly from reaction medium by the addition of water.

Low yields for methyl-substituted compounds **9h** and **9i** can be rationalized by presuming that electron donation to the site of displacement should retard the efficiency of an incoming nucleophile. Yields for the pyrimidoquinazolinones **12**, however, were generally lower, Again, methyl-substituted compounds **12e** and **12f** were inefficiently produced.

Extension of the double displacement methodology to the synthesis of imidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidines was accomplished as shown in Scheme III. Treatment of 2-chloropyridine-3-carbonyl chloride (**14**) with 2-methyl-thio-2-imidazoline hydroiodide and pyridine in methylene chloride provided the acyl imidazoline **15**, in 86% yield. Acylimidazoline **15** was then treated with neat hydrazines at elevated temperatures to give tricyclic compounds **16a-c** in 52-66% yield.

Since we have also been interested in the preparation of fused pyrazole ring systems [16-19], we extended the double displacement methodology to the synthesis of imidazo-[1,2-*a*]pyrazolo[3,4-*d*]pyrimidines, as shown in Scheme IV.

Scheme III

16 a, NRR = 4-morpholinyl
   b, NRR = 1-piperidinyl
   c, NRR = 1-homopiperidinyl
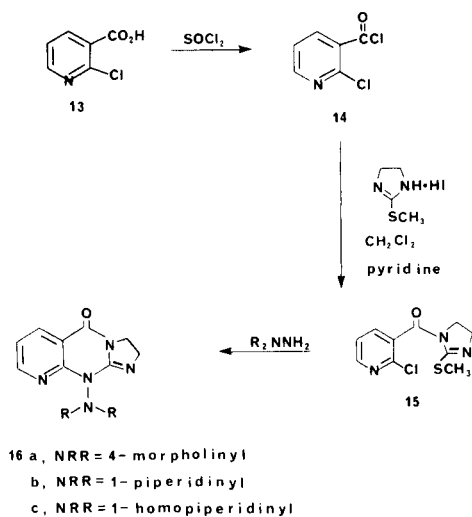
1-Methyl-5-nitropyrazole-4-carbonyl chloride (18) was treated with 2-methylthio-2-imidazoline hydroiodide and pyridine in methylene chloride to provide amide 19 in 72% yield. Cyclization of 19 with benzylamine in diglyme afforded tricyclic compound 20, in 35% yield [20]. Dehydrogenation of 20 with manganese dioxide in xylene afforded the fully aromatic imidazopyrazolopyrimidine 21, in 66% yield. Interestingly, we were able to prepare the isomer of 20 in which the benzyl group was at the 8-position. Reductive cyclization [21] of amide 19 with zinc and acetic acid gave a 72% yield of 1,6,7,8-tetrahydro-1-methyl-4H-imidazo[1,2-a]pyrazolo[3,4-d]pyrimidin-4-one (22).

Scheme IV
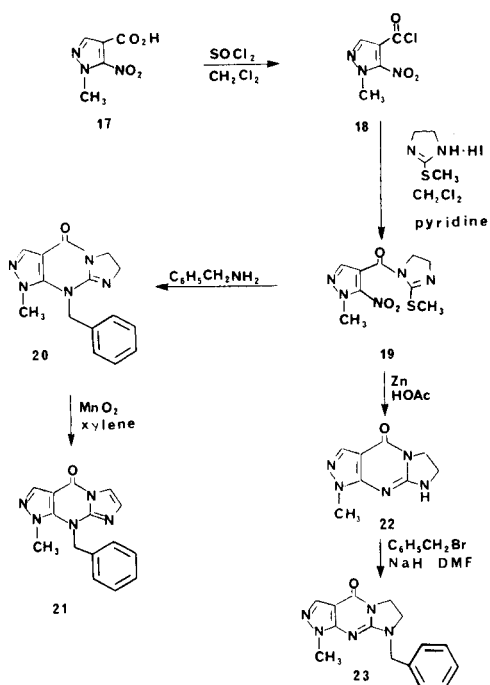
Alkylation of 22 with benzyl bromide and sodium hydride in dimethylformamide gave *exclusively* 23, in an isolated yield of 71%.

In an attempt to create a 7-membered ring *via* a double displacement reaction, we treated 8a with hydrazine monohydrate at reflux. Displacement of the imidazoline unit occurred to give 2-fluorobenzoic acid hydrazide (24)

The reaction of 8a with 1-methyl-1-phenylhydrazine is included in Scheme V since it, too, is anomalous. A solution of 8a and the hydrazine in diglyme was heated at reflux for 4.5 hours. After workup and flash chromatography, small amounts of 2,3-dihydroimidazo[2,1-b)quinazolin-5(10H)-one (27) and the corresponding 10-phenyl derivative 28 were isolated. No compound corresponding to those obtained using symmetrical 1,1-dialkyl hydrazines was isolated. Compounds 27 and 28 are interesting since they suggest that at some point in the reaction profile the 1-methyl-1-phenylhydrazine unit is ungergoing demethylation and N-N bond reductive cleavage under the reaction conditions. Formally, compounds 27 and 28 are products of double displacement of 8a with ammonia and aniline, respectively.

Scheme V
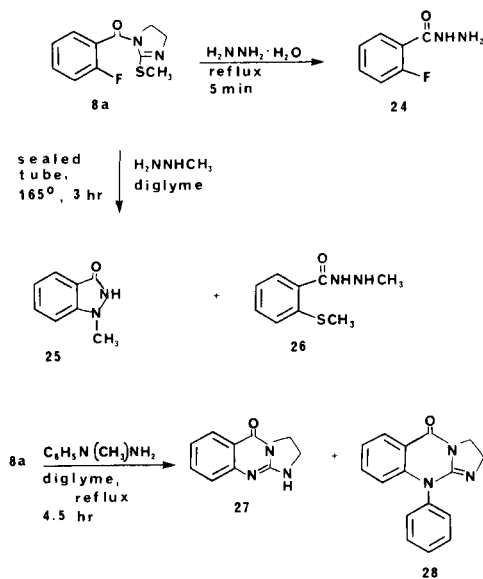
In summary, we have shown that the double displacement methodology is useful for preparing imidazo[2,1-b]-quinazolines, pyrimido[2,1-b]quinazolines, imidazo[1,2-a]-pyrido[2,3-d]pyrimidines, and imidazo[1,2-a]pyrazolo-[3,4-d]pyrimidines. Treatment of 1-(2-fluorobenzoyl)-2-methylthio-2-imidazoline (8a) with hydrazine hydrate or methylhydrazine did not lead to benzotriazepines.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with Perkin Elmer Model 727B and Model 1310 spectrophotometers, nmr

spectra with Varian EM-360A and Varian XL-300 spectrometers, and mass spectra with a Finnigan Model 4500 (electron impact and chemical ionization) mass spectrometer. Combustion analyses for C, H, and N were performed by Merrell Dow Analytical Laboratories, Cincinnati, OH.

Materials and Methods.

1-Methyl-5-nitropyrazole-4-carboxylic acid (**17**) was purchased from Maybridge Chemical Co., Trevillett Tintagel Cornwall PL 340HW, U.K. 2-Methylthio-2-imidazoline hydroiodide was purchased from Aldrich Chemical Co. 2-Methylthio-3,4,5,6-tetrahydropyrimidine hydroiodide (**10**), mp 146-147° (lit [23] mp 149-149.5°) was prepared in 90% yield using the procedure of McKay and Hatton [23]. Acid chlorides **4** (R = F, NO$_2$; R' = H, Cl, CH$_3$) were prepared by treating methylene chloride solutions of the corresponding carboxylic acids with excess thionyl chloride. Physical constants for the 1-benzoyl-4,5-dihydro-2-methylthio-1*H*-imidazoles **8** and 1-benzoyl-2-methylthio-1,4,5,6-tetrahydropyrimidines **11** are displayed in Table I. The method used for these compounds was the same as that described for **8a**, with the exceptions noted in Table I. Likewise, physical constants for imidazo[2,1-*b*]quinazolin-5(3*H*)-ones **9** and 6*H*-pyrimido[2,1-*b*]quinazolin-6-ones **12** are listed in Table II. The general procedure used for these compounds was similar to that described for **9a** with the exceptions noted in Table II.

Treatment of 2-Imidazolidinethione (**5**) with Benzoyl Chloride (**4a**).

To a slurry of 61.3 g (0.600 mole) of 2-imidazolidinethione and 4.75 g (0.600 mole) of pyridine in 1 liter of methylene chloride was added 84.3 g (0.600 mole) of benzoyl chloride over a 10-minute period. The mixture was at reflux by the end of the addition and reflux was continued for 15 hours. The mixture was cooled and concentrated and the resulting slurry was diluted with water (200 ml). The solid was collected, slurried with hot methanol (250 ml), and the yellow needles were collected to give 57.2 g (61%) of 1,3-bisbenzoyl-2-imidazolidinethione **7a**, mp 228-231°, mp 232-233° (methanol); ir (potassium bromide): 1675 (C=O) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 7.77-7.25 (m, 10H, aromatic), 4.18 (s, 4H, CH$_2$CH$_2$); ms: (70 eV, electron impact) m/e 310 (molecular ion).

Anal. Calcd. for C$_{17}$H$_{14}$N$_2$O$_3$S: C, 65.78; H, 4.55; N, 9.03. Found: C, 65.52; H, 4.61; N, 9.08.

The combined filtrates were concentrated and the resulting white solid was collected to give 17.9 g (14%) of 1-benzoyl-2-imidazolidinethione (**6a**), mp 148-149° (ethanol); ir (potassium bromide): 3180 (NH), 1670, 1660 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 9.66 (br s, 1H, NH, deuterium oxide-exchangeable), 7.63-7.20 (m, 5H, aromatic), 4.25-3.98 (m, 2H, C*H*$_2$CH$_2$NH), 3.70-3.40 (m, 2H, CH$_2$C*H*$_2$NH); ms: (70 eV, chemical ionization, methane) 207 (M$^+$ + 1), 235 (M$^+$ + 29), 247 (M$^+$ + 41).

Anal. Calcd. for C$_{10}$H$_{10}$N$_2$OS: C, 58.22; H, 4.89; N, 13.58. Found: C, 58.10; H, 4.95; N, 13.55.

Treatment of 2-Imidazolidinethione (**5**) with 2-Fluorobenzoyl Chloride (**4b**).

To a slurry of 30.6 g (0.300 mole) of 2-imidazolidinethione (**5**) and 47.5 g (0.600 mole) of pyridine in 500 ml of methylene chloride was added dropwise, over a 10-minute period, 47.6 g (0.300 mole) of 2-fluorobenzoyl chloride with no external cooling. At the end of the addition, reflux had initiated and solution had almost resulted. After 15 hours at reflux, the solution was cooled, washed with water (2 × 200 ml), dried (sodium sulfate), and concentrated to leave a slushy yellow solid. This solid was slurried with 200 ml of methanol and collected to give 33.1 g (64%) of 1,3-bis-(2-fluorobenzoyl)-2-imidazolidinethione (**7b**), mp 165-167°; ir (Nujol): 1675 (C=O) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 7.67-7.33 (m, 4H, aromatic), 7.33-7.04 (m, 4H, aromatic), 4.22 (s, 4H, CH$_2$CH$_2$); ms: (70 eV, electron impact) m/e 346 (molecular ion).

Anal. Cacld. for C$_{17}$H$_{12}$F$_2$N$_2$O$_2$S: C, 58.95; H, 3.49; N, 8.09. Found: C, 58.78; H, 3.65; N, 8.20.

The filtrate was concentrated to a small volume and the resulting solid was collected to give 3.14 g (4.7%) of 1-(2-fluorobenzoyl)-2-imidazolidinethione (**6b**), mp 153-156°; ir (Nujol): 3200 (NH), 1635 (C=O) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 9.79 (br s, 1H, NH, deuterium oxide-exchangeable), 7.62-7.00 (m, 4H, aromatic), 4.35-4.00 (m, 2H, CH$_2$),

3.75-3.43 (m, 2H, CH$_2$); ms: (70 eV, electron impact) m/e 224 (molecular ion).

Anal. Calcd. for C$_{10}$H$_9$FN$_2$OS: C, 53.55; H, 4.04; N, 12.49. Found: C, 53.34; H, 4.14; N, 12.72.

1-(2-Fluorobenzoyl)-2-methylthio-2-imidazoline (**8a**).

To a slurry of 122 g (0.500 mole) of 2-methylthio-2-imidazoline hydroiodide in 1 liter of methylene chloride was added 79.1 g (1.00 mole) of pyridine. A 79.3-g (0.500 mole) quantity of *o*-fluorobenzoyl chloride was then added dropwise over a 15-minute period (exothermic). The mixture was heated at reflux for 15 hours, cooled, and the white precipitate was collected. The precipitate was slurried with 1 liter of 1*N* sodium hydroxide and the insoluble white solid was collected, washed with water, and air-dried to give 63.3 g of **8a**, mp 99-101°. The original precipitate was washed with water (2 × 200 ml), dried (sodium sulfate), and concentrated to leave an oil which crystallized on standing to afford 42.6 g of additional **8a**, mp 98-100°. Total yield of **8a** was 106 g (89%), mp 100-102° (toluene-hexane); ir (potassium bromide): 1655 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.67-6.90 (m, 4H, aromatic), 3.94 (s, 4H, CH$_2$CH$_2$), 2.44 (s, 3H, CH$_3$); ms: (70 eV, electron impact) m/e 238 (molecular ion).

Anal. Calcd. for C$_{11}$H$_{11}$FN$_2$OS: C, 55.44; H, 4.65; N, 11.76. Found: C, 55.40; H, 4.66; N, 11.75.

2,10-Dihydro-10-(4-morpholinyl)imidazo[2,1-*b*]quinazolin-5(3*H*)-one (**9a**).

A solution of 10.0 g (42.0 mmoles) of **8a** in 50 ml of *N*-aminomorpholine was heated at reflux for 10 minutes. The clear solution deposited crystals on cooling. The mixture was diluted with water (100 ml) and the white, crystalline solid was collected, washed with water, and air-dried to give 8.47 g (74%) of **9a**, mp 250-251° (dimethylformamide-water); ir (potassium bromide): 1685 (C=O), 1640 (C=N) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 7.85 (dd, J = 7.8 Hz, J = 1.5 Hz, 1H, C6-H), 7.75 (d, J = 7.8 Hz, 1H, C9-H), 7.66 (ddd, J = 7.8 Hz, J = 7.3 Hz, J = 1.5 Hz, 1H, C8-H), 7.13 (ddd, J = 7.8 Hz, J = 7.3 Hz, J = 1.5 Hz, 1H, C7-H), 3.99 (m, 2H, C3-H$_2$), 3.66 (m, 2H, C2-H$_2$), 3.80-3.93 (m, 6H, CHNCH and CH$_2$OCH$_2$), 2.72 (d, 2H, J = 10.8 Hz, CHNCH); ms: (70 eV, electron impact) m/e 272 (molecular ion).

Anal. Calcd. for C$_{14}$H$_{16}$N$_4$O$_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.68; H, 5.99; N, 20.76.

2,10-Dihydro-10-(1-piperidinyl)imidazo[2,1-*b*]quinazolin-5(3*H*)-one (**9b**).

A solution of 10.0 g (42.0 mmoles) of **8a** and 25 ml of 1-aminopiperidine in 50 ml of 2-methoxyethyl ether (diglyme) was heated at reflux for 15 hours. The solution was diluted while hot with *ca.* 5 ml of water and allowed to cool. The resulting white needles were collected, washed with ethanol, and air-dried to give 8.10 g (71%) of **9b**, mp 229-231°: mp 229-230° (methanol); ir (potassium bromide): 1685 (C=O), 1642 (C=N) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 7.83 (dd, J = 7.3 Hz, J = 1.9 Hz, 1H, C6-H), 7.72-7.62 (m, 2H, C8-H and C-9H), 7.09 (ddd, J = 7.8 Hz, J = 7.3 Hz, J = 1.5 Hz, 1H, C7-H), 3.95-3.70 (m, 6H, CHNCH and C2,C3-CH$_2$CH$_2$), 2.80 (d, J = 10.3 Hz, 2H, CHNCH), 1.80-1.56 (m, 6H, remaining CH$_2$); ms: (70 eV, chemical ionization, methane) 271 (M$^+$ + 1), 299 (M$^+$ + 29), 311 (M$^+$ + 41).

Anal. Calcd. for C$_{15}$H$_{18}$N$_4$O: C, 66.66; H, 6.71; N, 20.73. Found: C, 66.39; H, 6.80; N, 20.87.

10-(Hexahydro-1*H*-azepin-1-yl)-2,10-dihydroimidazo[2,1-*b*]quinazolin-5(3*H*)-one (**9c**).

A solution of 10.0 g (42.0 mmoles) of **8a** in 50 ml of *N*-aminohomopiperidine was heated at reflux for 10 minutes. Upon cooling a white, crystalline solid formed. The mixture was diluted with water (100 ml) and the solid was collected, washed with water, and air-dried to give 9.03 g (76%) of **9c**, mp 206-208° (dimethylformamide-water); ir (potassium bromide): 1685 (C=O), 1642 (C=N) cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d$_6$): δ 7.83 (dd, J = 7.3 Hz, J = 1.5 Hz, 1H, C6-H), 7.75-7.60 (m, 2H, C8-H and C9-H), 7.10 (ddd, J = 7.8 Hz, J = 7.3 Hz, J = 1.5 Hz, 1H, C7-H), 4.00-3.75 (m, 4H, C2,C3-CH$_2$CH$_2$), 3.66 (m, 2H, CHNCH), 2.91 (m, 2H, CHNCH), 1.83-1.46 (m, 8H, remaining CH$_2$); ms: (70 eV, chemical ionization, methane) 285 (M$^+$ + 1), 313 (M$^+$ + 29), 325 (M$^+$ + 41).

Anal. Calcd. for $C_{16}H_{20}N_4O$: C, 67.58; H, 7.09; N, 19.71. Found: C, 67.60; H, 7.12; N, 19.81.

2,10-Dihydro-10-(dimethylamino)imidazo[2,1-b]quinazolin-5(3H)-one (9d).

A solution of 2.40 g (10.1 mmoles) of **8a** and 3 ml of 1,1-dimethylhydrazine in 6 ml of diglyme was heated at 165° for 3 hours in a sealed glass tube. The cooled solution was diluted with water and the resulting solid was collected and air-dried to give 1.80 g (77%) of **9d**, mp 197-198° (ethanol); ¹H nmr (deuteriochloroform): δ 8.05-7.83 (m, 1H, C6-H), 7.73-7.30 (m, 2H, C8-H and C9-H), 7.16-6.83 (m, 1H, C7-H), 3.97 (s, 4H, CH₂CH₂), 2.93 [s, 6H, N(CH₃)₂].

Anal. Calcd. for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.32; H, 6.15; N, 24.20.

2,10-Dihydro-10-(phenylmethyl)imidazo[2,1-b]quinazolin-5(3H)-one (9e).

A solution of 1.00 g (4.20 mmoles) of **8a** in 15 ml of benzylamine was heated at reflux for 10 minutes. The cloudy solution was cooled and the mixture was diluted with ether. The resulting white solid was collected, washed with water, and oven-dried to give 0.83 g (71%) of **9e**, mp 203-204° (lit [1] mp 203-205°); ¹H nmr (deuteriochloroform): δ 7.91 (dd, J = 7.9 Hz, J = 1.5 Hz, 1H, C6-H), 7.51 (ddd, J = 8.3 Hz, J = 7.3 Hz, J = 1.5 Hz, 1H, C8-H), 7.40-7.20 (m, 5H, phenyl), 7.08 (dd, J = 7.9 Hz, J = 7.3 Hz, 1H, C7-H), 7.03 (d, J = 8.3 Hz, 1H, C9-H), 5.30 (s, 2H, benzyl CH₂), 4.06 (t, J = 8.8 Hz, 2H, NCH₂), 3.79 (t, J = 8.8 Hz, 2H, NCH₂).

Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.54; H, 5.53; N, 14.99.

1-(2-Chloropyridine-3-carbonyl)-2-methylthio-2-imidazoline (15).

A mixture of 50.0 g (0.317 mole) of 2-chloropyridine-3-carboxylic acid (**13**) and 120 ml of thionyl chloride was heated at reflux for 3 hours and the resulting solution was concentrated to dryness. The resulting oil was twice diluted with methylene chloride and concentrated to dryness to give 55.4 (99%) of 2-chloropyridine-3-carbonyl chloride (**14**). This acid chloride was added to a mixture of 76.9 g (0.315 mole) of 2-methylthio-2-imidazoline hydroiodide, 1 ℓ of methylene chloride, and 63.7 g (0.630 mole) of triethylamine and the new mixture was heated at reflux for 16 hours. The solvent was removed by evaporation and the residue was stirred with water for 15 minutes. The white solid was collected by filtration and dried to give 69.2 g (86%) of **15**, mp 100-102° (ethanol-water); ¹H nmr (deuteriochloroform): δ 8.40 (dd, J = 5 Hz, J = 2 Hz, 1H, C6-H), 7.74 (dd, J = 7.5 Hz, J = 2 Hz, 1H, C4-H), 7.35 (dd, J = 7.5 Hz, J = 5 Hz, 1H, C5-H), 3.93 (s, 4H, CH₂CH₂), 2.42 (s, 3H, CH₃).

Anal. Calcd. for $C_{10}H_{10}ClN_3OS$: C, 46.97; H, 3.94; N, 16.43. Found: C, 46.95; H, 3.87; N, 16.71.

2,10-Dihydro-10-(4-morpholinyl)imidazo[1,2-a]pyrido[2,3-d]pyrimidin-5(3H)-one (16a).

A mixture of 5.00 g (19.5 mmoles) of **15** and 6.40 g (62.6 mmoles) of N-aminomorpholine was heated in an oil bath at 160° for 1 hour. The resulting mixture was cooled and partitioned between methylene chloride and water. The organic layer was dried (sodium sulfate) and concentrated. The crystalline residue was triturated with hexane and the solid was collected to give 2.75 g (52%) of **16a**, mp 225-226° (benzene-hexane); ¹H nmr (deuteriochloroform): δ 8.55 (dd, J = 4.9 Hz, J = 2.0 Hz, 1H, C8-H), 8.30 (dd, J = 7.7 Hz, J = 2.0 Hz, 1H, C6-H), 7.09 (dd, J = 7.7 Hz, J = 4.9 Hz, 1H, C7-H), 4.15-3.95 (m, 4H, C2-H₂ and C3-H₂), 3.95-3.85 (m, 6H, CH₂OCH₂ and CHNCH), 3.40-3.30 (m, 2H, CHNCH); ms: (70 eV, chemical ionization, methane) 274 (M⁺ + 1).

Anal. Calcd. for $C_{13}H_{15}N_5O_2$: C, 57.13; H, 5.53; N, 25.63. Found: C, 56.99; H, 5.54; N, 25.85.

2,10-Dihydro-10-(1-piperidinyl)imidazo[1,2-a]pyrido[2,3-d]pyrimidin-5(3H)-one (16b).

A mixture of 10.0 g (39.1 mmoles) of **15** and 11.4 g (0.114 mole) of 1-aminopiperidine was heated at 160° for 1 hour. The mixture was concentrated by Kugelrohr distillation and the residue was partitioned between methylene chloride and water. The organic layer was dried (sodium sulfate) and concentrated to a small volume. The resulting crystals

were collected to give 5.74 g (54%) of **16b**, mp 206-207° (benzene-hexane); ¹H nmr (deuteriochloroform): δ 8.55 (dd, J = 4.8 Hz, J = 2.0 Hz, 1H, C8-H), 8.28 (dd, J = 7.7 Hz, J = 2.0 Hz, 1H, C6-H), 7.05 (dd, J = 7.7 Hz, J = 4.8 Hz, 1H, C7-H), 4.13-3.97 (m, 4H, C2-H₂ and C3-H₂), 3.66-3.57 (m, 2H, CHNCH), 3.42-3.33 (m, 2H, CHNCH), 1.90-1.70 (m, 4H, 3'-CH₂ and 5'-CH₂), 1.65-1.40 (m, 2H, 4'-CH₂); ms: (70 eV, chemical ionization, methane) 272 (M⁺ + 1), 300 (M⁺ + 29).

Anal. Calcd. for $C_{14}H_{17}N_5O$: C, 61.97; H, 6.32; N, 25.81. Found: C, 61.89; H, 6.34; N, 25.83.

10-Hexahydro-1H-azepin-1-yl)-2,10-dihydroimidazo[1,2-a]pyrido[2,3-d]pyrimidin-5(3H)-one (16c).

A mixture of 10.0 g (39.1 mmoles) of **15** and 12.5 g (0.109 mole) of N-aminohomopiperidine was heated at 160° for 1 hour. Excess N-amino-homopiperidine was removed by Kugelrohr distillation and the residue was partitioned between methylene chloride and water. The organic layer was dried (sodium sulfate) and concentrated to leave 7.40 g (66%) of **16c**, mp 217-219° (benzene-hexane); ¹H nmr (deuteriochloroform): δ 8.55 (dd, J = 4.8 Hz, J = 2.0 Hz, 1H, C8-H), 8.28 (dd, J = 7.7 Hz, J = 2.0 Hz, 1H, C6-H), 7.04 (dd, J = 7.7 Hz, J = 4.8 Hz, 1H, C7-H), 4.14-3.97 (m, 4H, C2-H₂ and C3-H₂), 3.59-3.49 (m, 2H, CHNCH), 3.38-3.28 (m, 2H, CHNCH), 1.90-1.60 (m, 8H, NCH₂CH₂CH₂CH₂CH₂); ms: (70 eV, chemical ionization, methane) 286 (M⁺ + 1), 314 (M⁺ + 29).

Anal. Calcd. for $C_{15}H_{19}N_5O$: C, 63.14; H, 6.71; N, 24.55. Found: C, 63.18; H, 6.74; N, 24.75.

4-[(4,5-Dihydro-2-methylthio)-1-imidazolyl]-1-methyl-5-nitropyrazole (19).

To a slurry of 11.1 g (58.6 mmoles) of **18**, 16.1 g (66.0 mmoles) of 2-methylthio-2-imidazoline hydroiodide and 200 ml of methylene chloride was added, dropwise, 10.6 ml (131 mmoles) of pyridine. The reaction mixture was stirred at room temperature for 1 hour and the solvent was removed under reduced pressure. The residue was treated with hot water to provide a tan solid which was collected and recrystallized (dimethylformamide-water) to give 11.2 g (73%) of **19**, mp 130-132°; ¹H nmr (deuteriochloroform): δ 7.60 (s, 1H, C3-H), 4.30 (s, 3H, NCH₃), 3.90 (s, 4H, CH₂CH₂), 2.40 (s, 3H, SCH₃); ms: (70 eV, electron impact) m/e 269 (molecular ion).

Anal. Calcd. for $C_9H_{11}N_5O_2S$: C, 40.14; H, 4.12; N, 26.01. Found: C, 40.13; H, 4.15; N, 26.02.

1,6,7,9-Tetrahydro-1-methyl-9-(phenylmethyl)-4H-imidazo[1,2-a]pyrazolo[3,4-d]pyrimidin-4-one (20).

A solution of 6.70 g (24.9 mmoles) of **19** and 10.9 ml (0.100 mole) of benzylamine in 100 ml of diglyme was heated at reflux for 1 hour. The solution was concentrated under reduced pressure and collection of the resulting white solid afforded 1.30 g of pure **20**. Flash chromatography (95:5::dichloromethane:methane) of the concentrated filtrate gave an additional 0.80 g of **20**. Total yield of **20**, mp 209-211°, was 2.10 g (30%); ¹H nmr (deuteriochloroform): δ 7.75 (s, 1H, C3-H), 7.40-7.00 (m, 5H, phenyl), 5.40 (s, 2H, benzyl CH₂), 4.15-3.90 (m, 4H, CH₂CH₂), 3.75 (s, 3H, NCH₃); ms: (70 eV, electron impact) m/e 281 (molecular ion).

Anal. Calcd. for $C_{15}H_{15}N_5O$: C, 64.04; H, 5.37; N, 24.90. Found: C, 64.11; H, 5.12; N, 24.90.

1,9-Dihydro-1-methyl-9-(phenylmethyl)-4H-imidazo[1,2-a]pyrazolo[3,4-d]pyrimidin-4-one (21).

A mixture of 500 mg (1.78 mmoles) of **20** and 1.4 g (16 mmoles) of manganese dioxide (dried by azeotropic removal of water with benzene) and 160 ml of o-xylene was heated at reflux for 20 hours. The mixture was filtered while hot, the precipitate was washed with methylene chloride, and the filtrate was concentrated. Trituration of the residue with ether provided 300 mg (60%) of **21** as light yellow crystals, mp 166-168°; ¹H nmr (deuteriochloroform): δ 8.00 (s, 1H, C3-H), 7.60 (d, J = 2 Hz, C6-H), 7.45-7.00 (m, 5H, phenyl), 7.00 (d, J = 2 Hz, 1H, C7-H), 5.80 (s, 2H, CH₂), 3.95 (s, 3H, CH₃); ms: (70 eV, electron impact) m/e 279 (molecular ion).

Anal. Calcd. for $C_{15}H_{13}N_5O$: C, 64.50; H, 4.69; N, 25.08. Found: C, 64.45; H, 4.77; N, 25.14.

1,6,7,8-Tetrahydro-1-methyl-4H-imidazo[1,2-a]pyrazolo[3,4-d]pyrimidin-4-one (22).

To a warm solution of 11.2 g (41.6 mmoles) of 19 in 225 ml of acetic acid was added 16.8 g of zinc dust, in portions, with occasional ice bath cooling. After 30 minutes of stirring the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was triturated with water and the resulting white solid was collected, washed with water, and air-dried to give 5.20 g (65%) of 22, mp >290° (water); ^{1}H nmr (dimethyl sulfoxide-d₆): δ 8.10 (s, 1H, NH), 7.80 (s, 1H, C3-H), 4.10-4.00 (m, 2H, CH₂), 3.70 (s, 3H, NCH₃), 3.75-3.60 (m, 2H, CH₂); ms: (70 eV, chemical ionization) 192 (M⁺+1), 220 (M⁺+29), 232 (M⁺+41).

Anal. Calcd. for C₈H₁₁N₅O: C, 64.04; H, 5.37; N, 24.90. Found: C, 63.84; H, 5.46; N, 25.06.

1,6,7,8-Tetrahydro-1-methyl-8-(phenylmethyl)-4H-imidazo[1,2-a]pyrazolo-[3,4-d]pyrimidin-4-one (23).

To a mixture of 2.70 g (14.1 mmoles) of 22 in 60 ml of dimethylformamide was added 0.5 g (20 mmoles) of dry sodium hydride. The mixture was stirred for 15 minutes and 1.9 ml (16 mmoles) of benzyl bromide was added dropwise, with occasional ice bath cooling. After 15 hours the solvent was removed under reduced pressure and the residue was triturated with ether to provide 2.80 g (71%) of 23, mp 153-154° (ethanol-water); ^{1}H nmr (dimethyl sulfoxide-d₆): δ 7.80 (s, 1H, C3-H), 7.42-7.28 (m, 5H, phenyl), 4.60 (s, 2H, benzyl CH₂), 4.00 (t, 2H, CH₂), 3.75 (s, 3H, CH₃), 3.60 (t, 2H, CH₂); ms: (70 eV, electron impact) m/e 281 (molecular ion).

Anal. Calcd. for C₁₅H₁₅N₅O: C, 64.04; H, 5.37; N, 24.90. Found: C, 63.84; H, 5.46; N, 25.06.

Treatment of 8a with Hydrazine Hydrate.

A mixture of 1.00 g (4.20 mmoles) of 8a and 10 ml of hydrazine hydrate was heated at reflux for 5 minutes. The resulting solution was cooled, diluted with water (50 ml), and extracted with methylene chloride (3 × 30 ml). The organic layer was dried (sodium sulfate) and concentrated to leave 4.10 g (63%) of 2-fluorobenzoic acid hydrazide (24), mp 70-71° (lit [24] mp 72-73°); ^{1}H nmr (deuteriochloroform): δ 8.60-7.90 (m, 2H, aromatic plus deuterium oxide-exchangeable NHNH₂), 7.77-6.93 (m, 3H, aromatic), 4.30 (broad s, 2H, NH₂, deuterium oxide-exchangeable); ms: (70 eV, chemical ionization, methane) 155 (M⁺+1), 1.83 (M⁺+29), 195 (M⁺+41).

Treatment of 8a with Methylhydrazine.

A solution of 15.0 g (62.9 mmoles) of 8a and 11.6 g of methylhydrazine in 40 ml of diglyme was heated in a sealed glass tube at 165° for 3 hours. The solvent was removed by Kugelrohr distillation and the solid residue was triturated with water and collected to give 2.5 g of solid which was applied to flash chromatography silica gel (300 ml dry volume) and eluted with 3:2::ethyl acetate:hexane. Fractions containing the first component were collected to give 1.2 g (13%) of 1-methylindazol-3(2H)-one (25), mp 153-154° (lit [25] mp 153-154°); ^{1}H nmr (deuteriochloroform): δ 7.78 (m, 1H, C4-H), 7.44 (m, 1H, C6-H), 7.23 (m, 1H, C7-H), 7.09 (m, 1H, C5-H), 3.86 (s, 3H, CH₃); ms: (70 eV, electron impact) m/e 148 (molecular ion).

Fractions containing the second component were concentrated to leave 1.10 g (8.9%) of 2-(methylthio)benzoic acid 2-methylhydrazide (26), mp 119-120°; ^{1}H nmr (deuteriochloroform): δ 7.76 (broad s, 1H, amide NH), 7.55 (dd, 1H, C6-H), 7.42 (dt, 1H, C4-H), 7.32 (dd, 1H, C3-H), 7.22 (dt, 1H, C5-H), 2.77 (s, 3H, NCH₃), 2.48 (s, 3H, SCH₃); ms: (70 eV, chemical ionization, methane) 197 (M⁺+1), 225 (M⁺+29), 237 (M⁺+41).

Anal. Calcd. for C₉H₁₂N₂OS: C, 55.07; H, 6.16; N, 14.28. Found: C, 55.06; H, 6.08; N, 14.30.

Treatment of 8a with 1-Methyl-1-phenylhydrazine.

A mixture of 5.00 g (21.0 mmoles) of 8a, 7.70 g (63.0 mmoles) of 1-methyl-1-phenylhydrazine and 50 ml of diglyme was heated at reflux for 4.5 hours. The mixture was concentrated by Kugelrohr distillation and the residue was partitioned between methylene chloride and water. The organic layer was washed twice with water, dried (sodium sulfate), and concentrated. The resulting brown oil was triturated with ether to

give 500 mg of brown solid, which was a mixture of two components by tlc. Separation of this mixture by flash chromatography, using 9:1::chloroform:methanol as the eluant, gave 200 mg (5%) of 2,3-dihydro-imidazo[2,1-b]quinazolin-5(1H)-one (27), mp 229-230° dec (lit [1] mp 262-264°), as the faster moving component; ^{1}H nmr (deuterated trifluoroacetic acid): δ 8.33 (d, 1H, C6-H), 7.96 (dd, 1H, C8-H), 7.64 (dd, 1H, C7-H), 7.52 (d, 1H, C9-H), 4.62 (t, 2H, CH₂), 4.27 (t, 2H, CH₂); ms: (70 eV, chemical ionization, methane) 188 (M⁺+1), 216 (M⁺+29), 228 (M⁺+41).

Fractions containing the second component were concentrated to give 150 mg (3%) of 2,3-dihydro-10-phenylimidazo[2,1-b]quinazolin-5(10H)-one (28), mp 295-297° (methanol-water) (lit [1] mp 297-299°); ^{1}H nmr (deuterated trifluoroacetic acid): δ 8.43 (d, 1H, C6-H), 7.85 (m, 4H, C8-H and phenyl C3'-H, C4'-H, and C5'-H), 7.68 (dd, 1H, C7-H), 7.58 (m, 2H, C2'-H, and C5'-H), 6.90 (d, 1H, C9-H), 4.75 (t, 2H, CH₂), 4.20 (t, 2H, CH₂); ms: (70 eV, chemical ionization, methane) 264 (M⁺+1), 292 (M⁺+29), 304 (M⁺+41).

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m/e 320 (molecular ion).

  Anal. Calcd. for $C_{19}H_{20}N_4O$: C, 71.22; H, 6.29; N, 17.49. Found: C, 70.97; H, 6.39; N, 17.31.

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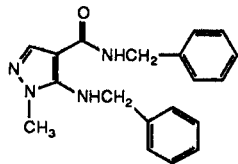
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