Synthesis and Herbicidal Activity of 1,2,3,4-Tetrahydro-1,3,5-triazino[1,2-*a*]benzimidazoles

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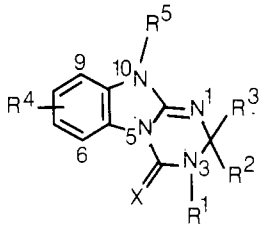
A series of novel 1,2,3,4-tetrahydro-1,3,5-triazino[1,2-*a*]benzimidazoles was synthesized by the general sequence (1) reaction of 2-aminobenzimidazoles with ketones or aldehydes to give Schiff bases, (2) condensation of the latter with isocyanates to give N^{10}-carbamoyl-1,2,3,4-tetrahydro-1,3,5-triazino-[1,2-*a*]benzimidazoles, and (3) hydrolysis of *N*-carbamoyl from the latter to give the parent heterocycles. Many compounds in this series showed pronounced broad-spectrum herbicidal activity, particularly against broadleaf weeds, postemergence, and on aquatic species. A 4-oxo function on the triazine ring was necessary for high herbicidal activity. Activity was generally highest for compounds with small alkyl substituents at the triazine C-2 and N-3 ring positions and was virtually eliminated by aromatic substituents at C-2.

The fungicidal and anthelmintic properties of certain 1,2,3,4-tetrahydro-1,3,5-triazino[1,2-*a*]benzimidazoles have long been known (Daum and Frohberger, 1977; Beard et al., 1977). We now report a series of such compounds represented by structure **1**, which is novel and possesses pronounced, broad-spectrum herbicidal activity. The compounds were particularly active against broadleaf weeds, postemergence, and on aquatic species (Ward and Berthold, 1985, Koerwer, 1983).



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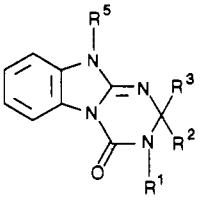
RESULTS AND DISCUSSION

Chemistry. The desired tricyclic compounds (X = O, S) were prepared via the Schiff bases **2**, which were isolated or treated in situ with 2 equiv of an isocyanate or isothiocyanate to afford the N^{10}-carbamoyl derivatives **3**. These compounds were cleaved thermally or with aqueous base to yield **4**, which presumably exists as a mixture of tautomers (Scheme I). Formation of the Schiff bases was generally accomplished by heating a mixture of the appropriate 2-aminobenzimidazole and a ketone or aldehyde in the presence of 3A molecular sieves. Although a cosolvent was employed in certain cases, the ketones were often used as the reaction solvent. In a typical experiment (method A), a solution of 2-aminobenzimidazole (Scheme I, R^4 = H) in acetone was heated at reflux in the presence of 3A molecular sieves. Aliquots of the reaction mixture were withdrawn at 1-day intervals, filtered, concentrated in vacuo, and examined by ^{1}H NMR spectroscopy. Sharp singlets were observed at δ 2.18 and 2.23, ascribable to the methyl proton resonances of the Schiff base **2** (R^2 = R^3 = CH_3). The integrals of these two peaks were observed to increase as the reaction proceeded and were used in conjunction with the aromatic proton integral to measure the progress of the reaction. At the end of 7 days, the reaction mixture was treated with 2 equiv of methyl isocyanate (MIC) to afford, after workup, a mixture of **6** and its MIC adduct **5** (see Table I). Two equivalents of the isocyanate was used due to the fact that carbamoylation of **4** occurs at a rate faster than formation of **4** from **2**. Treatment of the product mixture with 10% aqueous sodium hydroxide in THF afforded **6** in 42% yield based on 2-aminobenzimidazole. In a slight modification of method A, the Schiff base **2** (R^2, R^3 = CH_3) was treated in situ with *N*-chloroformamide (ClNHCHO; Coon, 1977), an isocyanic acid equivalent, to afford the known (Martin and Graubaum, 1979) compound **14** (Table I) in 30% yield.

As is evident from the above discussion, the rate of the reaction of 2-aminobenzimidazole with dialkyl ketones is exceedingly slow. Attempts to increase the rate of Schiff base formation by use of various catalysts and dehydrating agents were unsuccessful. However, the reaction of 2-aminobenzimidazole with *N*-isopropylidenepyrrolidinium perchlorate (Leonard and Paukstelis, 1963) in acetone for 23 h followed by treatment with 2 equiv of MIC afforded

Table I. Postemergent Herbicidal Activity of Selected 4-Oxo-1,2,3,4-tetrahydro-1,3,5-triazino[1,2-*a*]benzimidazoles



compd	R^1	R^2	R^3	R^5	HAI[a,b] broadleaf	HAI[a,b] grass
5	CH_3	CH_3	CH_3	$CONHCH_3$	71	24
6	CH_3	CH_3	CH_3	H	85	42
12	C_2H_5	CH_3	CH_3	H	85	21
13	n-C_3H_7	CH_3	CH_3	H	26	10
14	H	CH_3	CH_3	H	76	21
15	CH_3	CH_3	C_2H_5	H	80	18
16	CH_3	C_2H_5	C_2H_5	H	65	12
17	CH_3	CH_3	CH_3	$CONHC_2H_5$	82	26
18	CH_3	CH_3	CH_3	CONH-(n-C_3H_7)	87	32
19	CH_3	CH_3	CH_3	CONH-(i-C_3H_7)	91	29
20	m-$CH_3C_6H_4$	CH_3	CH_3	H	16	0

[a] See text for meaning of rating numbers. [b] Average of ratings at 1 and 2 lbs/acre.

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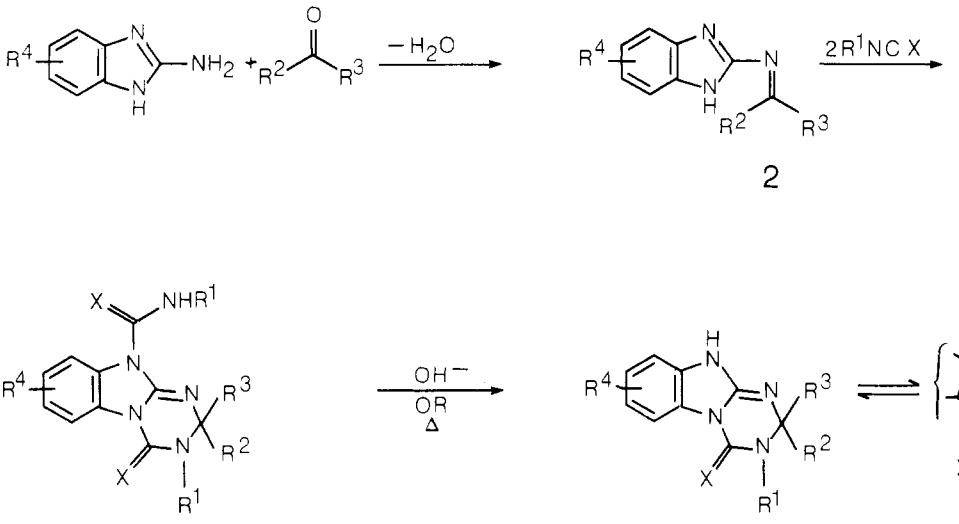
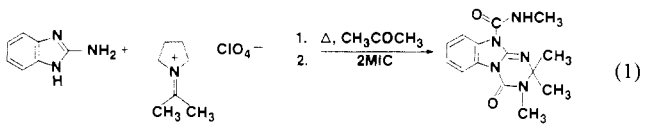
Scheme I



2

3 4

5 in 33% yield after chromatography (method B, eq 1). The shortened reaction time is presumably a consequence of the greater reactivity of the iminium salt as compared with acetone, resulting in more rapid formation of the Schiff base.

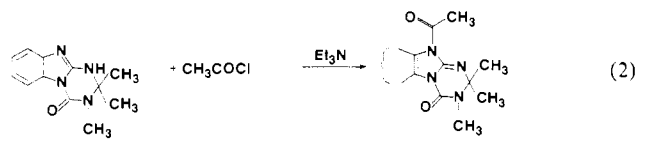


(1)

5

Assignments of the structures of 5 and 6 were made on the basis of their respective ^{1}H NMR spectra as the chemical shifts of the aromatic protons were particularly diagnostic. The spectrum of 6 ($CDCl_3$) showed a broad three-proton multiplet at δ 6.97–7.40 and a one-proton multiplet at δ 7.83–8.16. This downfield signal is due to the proton on C-6 that lies in the deshielding region of the C-4 carbonyl group (Graubaum and Martin, 1982, 1983).

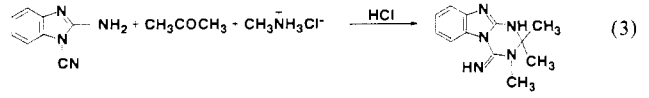
In addition to reacting with isocyanates, the parent heterocycles 1 (R^5 = H) could be readily substituted at N-10 by reaction with alkyl iodides, acid chlorides, and sulfonyl chlorides in the presence of a base. A typical example is the conversion of 6 to its N^{10}-acetyl derivative 7 by treatment with acetyl chloride in the presence of triethylamine (eq 2).



(2)

6 7

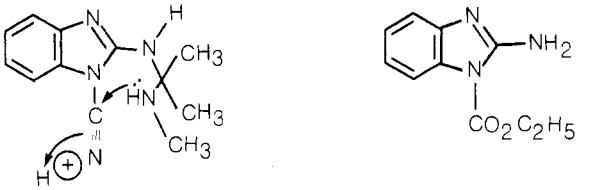
Compounds 1 wherein X = NH were prepared by the method of Payne (1966). In a typical example, 1-cyano-2-aminobenzimidazole (8) was treated with acetone in the presence of a catalytic amount of concentrated hydrochloric acid to afford imine 9 in 25% yield (eq 3). Al-



(3)

8 9

though its mechanism is unknown, the reaction may proceed through the intermediate aminal 10. Interestingly, attempts to carry out an analogous transformation employing the carboethoxy-substituted benzimidazole 11 failed to produce compound 6.

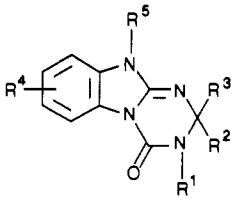


10 11

Biology. *Test Methods.* Compounds were evaluated as preemergence, postemergence, and aquatic herbicides. The test plants (terrestrial) were mustard (*Brassica kaber*), teaweed (*Sida spinosa*), sicklepod (*Cassia obtusifolia*), coffeeweed (*Sesbania exaltata*), field bindweed (*Convolvulus arvensis*), velvetleaf (*Abutilon theophrasti*), crabgrass (*Digitaria spp.*), giant foxtail (*Setaria faberi*), wild oats (*Avena fatua*), cheatgrass (*Bromus secalinus*), and barnyard grass (*Echinochloa crus-galli*). The aquatic test plants were duckweed (*Lemna minor*), *Salvinia rotundifolia*, *Elodea canadenis*, *Potamogeton pectinatus*, and *algae*. In the preemergence tests, the soil was sprayed with a solution of the test compound in acetone immediately after the seeds were planted. The compounds were applied at the rate of 8 lbs/acre of soil surface except where otherwise indicated in the tables. Approximately 3 weeks after spraying, the herbicidal activity of the compound was determined by visual observation of the treated areas in comparison with untreated controls. These observations are reported on a scale of 0–10, where 0 = no effect and 10 = 100% control of plant growth. In addition, the herbicidal effects were noted with respect to growth inhibition (G), burn (B), necrosis (N), emergence reduction (E), and chlorosis (C).

In the postemergence tests, the soil and developing plants were sprayed about 2 weeks after the seeds were sown at rates of 1, 2, and 8 lbs/acre as indicated in the tables. The postemergence activity is reported in Tables I and II. In Table II, activity is reported on a scale of 0–10 as described above. In Table I, the broadleaf herbicide activity index (HAI-Broadleaf) values are averages of percent kill and percent growth inhibition for five broad-

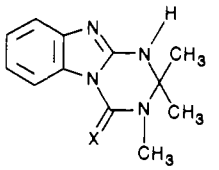
Table II. Terrestrial Herbicidal Activity of Selected 4-Oxo-1,2,3,4-tetrahydro-1,3,5-triazino[1,2-*a*]benzimidazoles[a]



						test plants[b]							
						mustard		teaweed		crabgrass		giant foxtail	
compd	R^1	R^2	R^3	R^4	R^5	post	pre	post	pre	post	pre	post	pre
7	CH_3	CH_3	CH_3	H	CH_3CO	10B	10N	10B	10N	10B	10N	10B	0
22	CH_3	CH_3	CH_3	7,8-$(CH_3)_2$	H	8N	2N	10N	3E	5N	7G	0	0
23	CH_3	CH_3	CH_3	H	CH_3	10B	8G	10G	10E	10B	4G	10B	5G
24	CH_3	CH_3	CH_3	H	CH_3SO_2	10N	10N	10G	10N	10N	10N	10N	10N
25	CH_3	2,4-$Cl_2C_6H_3$	H	H	H	0	0	0	0	0	2G	0	0
26	CH_3	$-(CH_2)_4-$		H	H	10N	9G	0	0	5N	0	0	0
27	n-C_4H_9	CH_3	CH_3	H	H	10N	9G	0	9G	2G	9G	0	8N

[a] 8 lbs/acre. [b] Herbicidal effects: G, growth inhibition; B, burn; N, necrosis; E, emergence reduction; C, chlorosis.

Table III. Effect of the Group X on Herbicidal Activity



		mustard		teaweed		crabgrass		giant foxtail	
compd	X	post	pre	post	pre	post	pre	post	pre
6[a]	O	10B	10N	10B	10N	10B	10N	4B	3N
9[b]	NH	0	0	0	0	0	0	0	0
21[b]	S	10N	5G	10N	2G	10N	10E	0	0

[a] 2 lbs/acre. [b] 8 lbs/acre.

leaf weeds (sicklepod, coffeeweed, field bindweed, teaweed, velvetleaf). The analogous values for grassy weeds are averages for three species (wild oats, cheatgrass, barnyard grass).

In the aquatic tests, a solution prepared by dissolving 15 mg of the test compound in acetone was added to 3 L of water in a large glass jar to provide a concentration of 5 ppm. Samples of the various aquatic weeds described above were placed in each jar. The jars were maintained at about 23 °C for 3 weeks after which time the results were recorded in terms of a scale ranging from 0 (no injury) to 10 (complete kill).

Terrestrial Herbicidal Activity (Tables I–III). As R^1 becomes larger than methyl, herbicidal activity decreases (compare **6** with **13**; Table I) with a sharp decline in activity observed between R^1 = ethyl and R^1 = *n*-propyl (compare **12** with **13**). Interestingly, when R^1 = H, activity is not enhanced but is decreased (compare **6** with **14**). Compounds wherein R^1, R^2 = methyl generally show better activity than those having larger alkyl substituents when other substituents are identical (compare **6** with **15**, **16**, and **26**), but the introduction of an aromatic substituent at R^1, R^2, or R^3 virtually eliminates activity (**20**, **25**). When R^5 = *N*-alkylcarbamoyl, broadleaf activity is not greatly affected; however, the moderate activity against grassy weeds is further weakened by such substitutions (compare **6** with **17–19**). Replacement of substituent X = O with X = S caused a decrease in preemergent activity in three of the four species, while X = NH abolished activity (Table III).

Aquatic Herbicidal Activity (Table IV). While there is little or no correlation between herbicidal activity toward terrestrial vegetation and activity against aquatic plants

Table IV. Aquatic Herbicidal Activity of Selected 1,2,3,4-Tetrahydro-1,3,5-triazino[1,2-*a*]benzimidazoles[a]

	test plants				
compd[b]	duckweed	*Salvinia*	*Elodea*	*Potamogeton*	*Algae*
5	10	10	10	3	0
6	10	10	10	0	10
7	10	10	0	3	0
12	6	10	10	3	10
13	3	10	3	0	0
14	10	10	6	0	0
15	10	10	10	3	0
16	10	10	6	8	0
17	10	10	10	0	10
18	10	10	10	3	10
19	10	10	0	0	10
21	3	10	3	3	0
22	10	10	10	3	10
23	6	10	0	3	0
24	10	10	8	8	0
26	3	10	0	0	0
27	0	10	3	0	0

[a] Relative aquatic activity at 5 ppm. See the text for the meaning of rating numbers. [b] See Tables I–III for structural key.

for many classes of compounds (Frank et al., 1963), our compounds displayed excellent aquatic activity. In general, the best compounds had R^1, R^2, and R^3 = methyl, and certain structure–activity trends paralleled those observed for terrestrial plants. For example, activity against duckweed, *Elodea*, and *algae* dropped off as the size of R^1 increased above methyl (**6**, **12**, **13**, **27**) as did activity against *Elodea* and *algae* when R^2, R^3 were larger than methyl (**15**, **16**, **26**). As in the terrestrial tests, a decrease

in the size of R^1 from methyl to hydrogen (14) lowered aquatic activity as reflected in the activity against *Elodea* and *algae*. The effect of replacing X = O with X = S also paralleled that observed in terrestrial tests as a large decrease in activity against all species except *Salvinia* was observed (compare **6** and **21**).

While *Salvinia* was most susceptible in the tests toward the entire class of compounds, *Potamogeton* was the least susceptible. Compounds that showed activity against *Potamogeton* were found among both the weaker and the stronger terrestrial herbicides with no clear pattern discernible (compare **6**, **16**, and **22**).

EXPERIMENTAL SECTION

All novel compounds were characterized by NMR and IR spectral analyses and elemental analysis. The melting points are uncorrected. ^{1}H NMR spectra were obtained with a Varian EM-360A spectrometer using tetramethylsilane (Me_4Si) as an internal standard. ^{13}C NMR spectra were obtained with a Varian XL-100 spectrometer using Me_4Si as an internal standard. Infrared spectra were recorded on a Perkin-elmer 197 or Beckman Acculab 2 spectrometer. Ultraviolet spectra were recorded on a Perkin-Elmer 202 spectrometer. Elemental analyses were obtained by the Union Carbide Analytical Group at the South Charleston, WV, Technical Center. Supplementary material containing physical properties is available (see paragraph at end of paper regarding supplementary material).

1,2-Dihydro-2,2,3-trimethyl-1,3,5-triazino[1,2-*a*]benzimidazol-4(3*H*)-one (6; Method A). A 1-L, round-bottomed flask containing a magnetic stirring bar was charged with 16 g (0.12 mol) of 2-aminobenzimidazole, 500 mL of acetone, and 16 g of 3A molecular sieves. The flask was fitted with a reflux condenser bearing a $CaSO_4$ drying tube after which the reaction mixture was stirred and heated at reflux. An additional 8 g of sieves was added on the second and fifth days of heating. Aliquots of the reaction mixture were withdrawn at 24-h intervals, filtered, concentrated in vacuo, and examined by NMR spectroscopy. After 7 days, the reaction was 58% complete. The reaction mixture was cooled to room temperature, and methyl isocyanate (13.7 g, 0.24 mol) was added rapidly via syringe. The resulting mixture was stirred overnight at room temperature after which time it was concentrated under reduced pressure to afford a brittle solid. The solid was broken up, slurried in hexane, and transferred into a Soxhlet extraction thimble. The thimble was placed in an extractor fitted to a 500-mL, round-bottomed flask containing a magnetic stirring bar and 400 mL of hexane. The material in the thimble was extracted until TLC (silica, 80:2:1 $CHCl_3$–MeOH–NH_4OH) showed none of the desired products remained (from 2 to 6 days). The solids that had precipitated in the extraction pot were collected with suction, and the resulting filtrate was concentrated to provide an additional small amount of material. The combined solids consisted of 14.9 g of a mixture of **6** and its N^{10}-methylcarbamoyl precursor **5**, ≥0.052 mol of tricyclic products (43%).

The mixture was charged to a 500-mL round-bottomed flask containing a magnetic stirring bar. THF (300 mL) was added followed by 30 mL of 10% aqueous sodium hydroxide. The resulting heterogeneous mixture was stirred at room temperature for 6.5 h after which time TLC showed that only a trace of the N^{10}-methylcarbamoyl material remained. The reaction mixture was transferred to a separatory funnel and washed with brine (3×). The organic phase was dried over potassium carbonate and concentrated under reduced pressure to afford 11.6 g of crude product **6** as a brown solid (42% yield based on 2-aminobenzimidazole). This material was recrystallized from acetone to yield 6.9 g of pure material. An analytical sample prepared as described above sintered at 206 °C and had a melting point of 209 °C dec: ^{1}H NMR (δ, $CDCl_3$) 1.73 (s, 6 H, *gem*-dimethyls), 3.12 (s, 3 H, *N*-CH_3), 6.96–7.40 (m, 3 H, aromatic H), 7.83–8.16 (m, 1 H, C-6 aromatic H); IR ($CHCl_3$) 3100–3200 (br, NH str), 1710 (C=O str), 1660 (C=N str), 1620, 1600, 1500, 1460, 1420, 1380, 1310, 1290, 1230, 1170, 1140, 1100, 1050, 890 cm^{-1}; UV (EtOH) λ_{max} 282 nm (ϵ 7600), 287 (ϵ 7830); ^{13}C NMR (δ, $CDCl_3$) 27.0 (*gem*-dimethyls), 27.8 (*N*-CH_3), 71.6 [C-$(CH_3)_2$], 113.9, 115.3, 120.3, 123.9 (aromatic carbons bearing H), 130.6, 142.2, 151.6 (aromatic carbons without H), 148.6, (C=O). Anal. Calcd for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.47; H, 6.16; N, 24.24.

4-Oxo-2,3,4,10-tetrahydro-*N*,2,2,3-tetramethyl-1,3,5-triazino[1,2-*a*]benzimidazole-10-carboxamide (5; Method B). To a stirred solution of 2 g (0.015 mol) of 2-aminobenzimidazole in 50 mL of acetone was added a solution of 2.99 g (0.015 mol) of *N*-isopropylidenepyrrolidinium perchlorate in acetone, in one portion, followed by an 8-g portion of 3A molecular sieves. The resulting mixture was heated under reflux with stirring for approximately 23 h, allowed to cool, treated with 1.71 g (0.03 mol) of methyl isocyanate, and stirred overnight at room temperature. The reaction mixture was filtered and the filtrate concentrated under reduced pressure. The resulting residue was taken up in chloroform, washed with water, dried ($MgSO_4$), and concentrated to give 3.4 g of a dark oil that was purified on a high-pressure liquid chromatograph, eluting with CH_2Cl_2–CH_3OH (97.6:2.4, v/v), giving 1.25 g (33% yield) of **5**: mp 164 °C dec; ^{1}H NMR (δ, $CDCl_3$) 1.60 (s, 6 H), 2.82–3.17 (m, 6 H), 6.96–7.36 (m, 2 H), 7.71–8.05 (m, 1 H), 8.05–8.38 (m, 1 H), 9.00–9.50 (br, 1 H); IR (KBr), 3400, 3200, 3050, 2975, 2925, 1710, (C=O str) 1560, 1470, 1410, 1360, 1290, 1200, 1180, 1160, 1000, 750, 690 cm^{-1}. Anal. Calcd for $C_{14}H_{17}N_5O_2$: C, 58.52; H, 5.97; N 24.38. Found: C, 58.60; H, 5.91; N, 24.04.

10-Acetyl-2,10-dihydro-2,2,3-trimethyl-1,3,5-triazino[1,2-*a*]benzimidazol-4(3*H*)-one (7). A 250-mL, round-bottomed flask containing a magnetic stirring bar was charged with 2.45 g (0.0106 mole) of **6**, 150 mL of acetone, and 1.53 mL of triethylamine. Acetyl chloride (0.86 g, 0.0110 mol) was added rapidly via syringe to the resulting solution. The mixture was stirred for 2 h at room temperature after which time a white precipitate of triethylammonium hydrochloride was visible. Examination of the reaction mixture by TLC (silica 80:2:1, $CHCl_3$–CH_3OH–NH_4OH) showed that only a trace of starting material remained. The mixture was concentrated in vacuo, and the resulting solid was taken up in methylene chloride. The resulting solution was washed with water (3×) followed by brine, then dried ($MgSO_4$), and concentrated under reduced pressure to afford 1.5 g (52% yield) of **7** as a white solid that was analytically pure: mp 159–162 °C; ^{1}H NMR (δ, $CDCl_3$) 1.57 (s, 6 H, *gem*-methyls), 2.70 (s, 3 H, $COCH_3$), 3.03 (s, 3 H, *N*-CH_3), 6.93–7.37 (m, 2 H, aromatic H), 7.77–8.07 (m, 1 H, C-6 aromatic H), 8.07–8.40 (m, 1 H, C-9 aromatic H); IR ($CHCl_3$) 3000, 1720 (C=O str), 1600, 1480, 1380, 1350, 1290, 1190, 1150 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.70; H, 5.71; N, 20.55.

1,2-Dihydro-2,2,3-trimethyl-1,2,5-triazino[1,2-*a*]benzimidazol-4(3*H*)-imine (9). A 500-mL, round-bottomed, four-necked flask fitted with a mechanical stirrer, thermometer, glass stopper, and a reflux condenser was charged with 7.9 g (0.05 mol) of 1-cyano-2-aminobenz-

imidazole (Pellizari and Gaiter, 1918), 3.4 g (0.05 mol) of methylammonium hydrochloride, 0.3 g of concentrated hydrochloric acid, and 300 mL of acetone. The resulting mixture was stirred and heated at 40–45 °C for 18 h after which time it was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in water, and the solution was adjusted to pH 6.0–6.8 with 10% sodium hydroxide. A white precipitate formed and was collected with suction. This material was dried at room temperature to afford 9.0 g (68% yield) of the hydrochloride of **9** as a white solid: mp 188–190 °C; IR (KBr) 3300, 3195, 2950, 1667, 1626, 1602, 1587, 1522, 1424, 1387, 1366, 742 cm^{-1}.

The salt was dissolved in 5% HCl, and the resulting solution was filtered. The filtrate was treated with an excess of saturated aqueous $NaHCO_3$ to afford **9** as a white solid: ^{13}C NMR (δ, $CDCl_3$) 30.0 (*gem*-dimethyls and *N*-CH_3), 69.5 [$C(CH_3)_2$], 111.0, 116.7, 120.3, 124.0 (aromatic carbons bearing H), 128.7, 143.5 (aromatic carbons without H), 143.8 (C=N), 153.5 (aromatic carbon without H). Anal. Calcd for $C_{12}H_{15}N_5$: C, 62.9; H, 6.6; N, 30.5. Found: C, 62.1; H, 6.3; N, 30.2.

1,2-Dihydro-2,2-dimethyl-1,3,5-triazino[1,2-*a*]benzimidazol-4(3*H*)-one (14). A mixture of 16 g (0.12 mol) of 2-aminobenzimidazole, 100 mL of acetone, and 16 g of 3A molecular sieves was stirred and heated under reflux, adding 8 g of additional sieves after 24 h. Refluxing was continued for a total of 3 days, after which the mixture was allowed to cool and a solution of 4.77 g (0.06 mol) of *N*-chloroformamide in 25 mL of acetone was added dropwise with stirring. The mixture warmed to the reflux point several times, and the rate of *N*-chloroformamide addition was adjusted to keep the temperature just below the reflux point. An additional 50 mL of acetone was added to facilitate stirring of the thickening reaction mixture. Upon completion of the feed, the reaction flask was fitted with a drying tube and the mixture was stirred for 3 days at room temperature. The reaction mixture was then evaporated under reduced pressure to give 9.3 g of a tan solid that was extracted with boiling acetone to separate an insoluble fraction, and the acetone solution was evaporated to give the crude solid product. This material was chromatographed on silica, eluting with $CHCl_3$–CH_3OH (80:5). Fractions 3–8 were combined and evaporated to give 3.9 g of product: mp 178–180 °C dec [lit. (Martin and Graubaum, 1979) mp 218 °C from EtOH]; ^1H NMR (δ, Me_2SO-d_6) 1.50 (s, 6 H), 6.87–7.47 (m, 3 H), 7.63–7.97 (m, 1 H), 8.58 (br, 2 H); IR (KBr) 3400 (br), 3225, 3075, 2975, 2875, 1720, 1630, 1600, 1580, 1460, 1375, 1290, 1270, 1230, 1180, 1140, 1010, 760, 740 cm^{-1}. Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.09; H, 5.60; N, 25.91. Found: C, 61.00, H, 5.49; N, 25.38.

***N*-Ethyl-4-oxo-2,3,4,10-tetrahydro-2,2,3-trimethyl-1,3,5-triazino[1,2-*a*]benzimidazole-10-carboxamide (17).** A 250-mL, round-bottomed flask containing a magnetic stirring bar was charged with 2.6 g (0.0113 mol) of compound **6** and 150 mL of acetone. To the resulting solution were added three drops of triethylamine and 0.78 g (0.011 mol) of ethyl isocyanate. The reaction mixture was stirred for 1 h at room temperature after which time TLC (silica, 80:2:1 $CHCl_3$–CH_3OH–NH_4OH) showed that reaction was complete. The mixture was concentrated under reduced pressure to afford 3.2 g (96%) of analytically pure **17**: mp 127–131 °C; ^1H NMR ($CDCl_3$) 1.23 (t, 3 H, J = 7 Hz), 1.60 (s, 6 H), 3.07 (s, 3 H), 3.17–3.73 (m, 2 H), 6.93–7.33 (m, 2 H), 7.70–8.07 (m, 1 H), 8.07–8.42 (m, 1 H), 9.12–9.63 (br, 1 H); IR ($CHCl_3$) 3225 (br), 2975, 1720–1710 (sh), 1560, 1475, 1420, 1380, 1290, 1200, 1170, 1010, 720 cm^{-1}. Anal. Calcd for $C_{15}H_{19}N_5O_2$: C, 59.78; H, 6.35; N, 23.24. Found: C, 59.82; H, 6.39; N, 23.43.

1,2-Dihydro-2,2,3-trimethyl-1,3,5-triazino[1,2-*a*]benzimidazole-4(3*H*)-thione (21). The procedure used was that described above in method A except that methyl isothiocyanate was used instead of MIC. In this case, a N^{10}-methylthiocarbamoyl derivative was not obtained and compound **21** was recovered directly from the Soxhlet extraction and recrystallized from acetone to give crystals: mp 186 °C dec; ^1H NMR (δ, $CDCl_3$) 1.75 (s, 6 H, *gem*-dimethyls), 3.53 (s, 3 H, *N*-CH_3), 6.90–7.37 (m, 3 H, aromatic H), 8.60–9.00 (m, 1 H, aromatic H); ^{13}C NMR (δ, $CDCl_3$) 27.0 (*gem*-dimethyls), 34.0 (*N*-CH_3), 73.0 [$C(CH_3)_2$], 115.5, 117.0, 121.0, 124.9 (aromatic carbons bearing H), 132.5, 142.9, 149.5 (aromatic carbons without H), 174.0 (C=S); IR ($CHCl_3$) 3300–2700 (br, NH), 1670 (C=N str), 1590, 1491, 1455, 1404, 1365, 1325, 1268, 1232, 1172, 1152, 1138, 1121, 1088, 1043, 1015, 972, 885, 752, 735 cm^{-1}. Anal. Calcd for $C_{12}H_{14}N_4S$: C, 58.51; H, 5.73; N, 22.75. Found: C, 58.65; H, 5.64; N, 22.98.

2-(2,4-Dichlorophenyl)-1,2-dihydro-3-methyl-1,3,5-triazino[1,2-*a*]benzimidazol-4(3*H*)-one (25). A 100-mL, round-bottomed flask containing a magnetic stirring bar was charged with 10 g (0.0751 mol) of 2-aminobenzimidazole, 13.2 g (0.0754 mol) of 2,4-dichlorobenzaldehyde, and 125 mL of absolute ethanol. The mixture was heated at reflux for 24 h after which time the reaction mixture was cooled to room temperature. A yellow solid crystallized from the reaction mixture and was collected with suction and washed with cold methanol. Three more crops of solid were similarly collected to afford a combined yield of 12.22 g (56%) of Schiff base **2** (R^2 = H, R^3 = 2,4-$Cl_2C_6H_3$): mp 234–235.5 °C; ^1H NMR (δ, Me_2SO-d_6 + $CDCl_3$) 3.2 (s, 1 H, exchangeable), 7.05–8.40 (m, 7 H), 9.78 (s, 1 H); IR (KBr) 1609, 1582, 1430, 1096, 1050, 882, 850, 737 cm^{-1}. Anal. Calcd for $C_{14}H_9Cl_2N_3$: C, 57.95; H, 3.13; N, 14.48. Found: C, 58.10; H, 2.91; N, 14.48.

A 250-mL, Erlenmeyer flask was charged with 7 g (0.024 mol) of the above Schiff base and 135 mL of dry THF. To the resulting solution was added 1.5 mL of triethylamine and 1.36 g (0.024 mol) of methyl isocyanate. The mixture was allowed to stand for 72 h at room temperature after which time a yellow solid was collected with suction to afford 2.4 g (29%) of **25**: mp 158–162 °C; ^1H NMR (δ, Me_2SO-d_6) 2.83 (s, 3 H), 6.37 (s, 1 H), 6.90–8.00 (m, 7 H); IR (KBr) 3170, 1724 (C=O str), 1590, 1390, 1200, 1140, 1100, 816, 760 cm^{-1}. Anal. Calcd for $C_{16}H_{12}Cl_2N_4O$: C, 55.35; H, 3.49; N, 16.14. Found: C, 54.96; H, 3.28; N, 16.03.

Registry No. **5**, 87575-60-8; **6**, 87589-82-0; **7**, 87575-74-4; **8**, 55179-78-7; **9**, 104576-58-1; **10**, 104576-59-2; **11**, 52938-06-4; **12**, 87575-61-9; **13**, 87575-63-1; **14**, 71109-15-4; **15**, 87575-66-4; **16**, 87575-79-9; **17**, 87575-68-6; **18**, 87575-69-7; **19**, 87575-70-0; **20**, 104576-60-5; **21**, 87575-86-8; **22**, 104576-61-6; **23**, 87575-76-6; **24**, 87575-85-7; **25**, 104576-62-7; **26**, 87575-83-5; **27**, 87575-64-2; MeNCS, 624-83-9; $MeNH_3^+Cl^-$, 593-51-1; HCONHCl, 52175-99-2; 2-aminobenzimidazole, 934-32-7.

Supplementary Material Available: Table V, listing the physical properties for compounds **12**, **13**, **15**, **16**, **18**, **20**, **22–24**, **26**, and **27** (1 page). Ordering information is given on any current masthead page.

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Effect of Processing on the Phytic Acid Content of Wheat Products

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The effect of processing on the phytic acid content of wheat and wheat products has been studied. Phytic acid is reduced significantly during the dough resting period at room temperature and on baking local leavened and unleavened flat breads. Addition of sodium bicarbonate for the preparation of Nan reduces the loss of phytic acid during the dough resting period. Roasting of wheat and preparation of Dalya (wheat porridge) result in reduction of phytic acid by 25 and 87.87%, respectively. Phytic acid is destroyed by 80.00–85.00% during the process of preparation of puri.

INTRODUCTION

Phytic acid is widely distributed in nature, and a large part of phosphorus in cereals and legumes is present in this form (Kent Jones and Amos, 1967). It is important for animal and human nutrition (Nelson, 1967; Taylor, 1965; McCance and Widdowson, 1942; Harrison and Mellanby; 1939, O'Dell and Sevage, 1960; Sharpe et al., 1950, Reinhold et al., 1973; Davies and Olpin, 1979; Oberleas, 1963), because of its ability to chelate several metals and thereby reduce their availability. Iron and zinc deficiencies occur in populations that subsist on unleavened whole-grain bread and rely on it as a primary source of these minerals. Deficiencies have been attributed to the presence of phytates (Reinhold et al., 1973; Oberleas, 1963; Reinhold, 1971; Haghshenass et al., 1972; Bruce and Callow, 1934). It causes rickets and bone deformation in young dogs (Harrison and Mellanby, 1939; Bruce and Callow, 1934).

Processing of cereals and legumes significantly reduces their phytic acid content. It has been reported that phytic acid conent is reduced during the process of baking leavened and unleavened Iranian flat breads (Ter-Sarkissian et al., 1974). According to Faridi et al. (1983), phytic acid of Iranian flat breads is reduced and the zinc availability is improved. It has been reported that phytic acid is reduced significantly during bread making (Pringle and Moran, 1942; Harland and Harland, 1980). No destruction of phytic acid takes place during the dough resting time and Chapati making process (Mehdi and Abrol, 1972). Cooking peas results in 13% phytate reduction (Beal and Mehta, 1985).

Wheat is the staple diet of Pakistan and is mainly consumed as leavened and unleavened flat breads, i.e. Chapati, Roti, and Nan. This paper deals with the effect of processing on the phytic acid content of wheat for the preparation of Pakistani leavened and unleavened flat breads and other wheat products.

EXPERIMENTAL SECTION

Materials and Methods. *Description of Pakistani Flat Breads. Chapati.* It is a round unleavened flat bread and is prepared from whole-wheat flour. The dough is covered with a moist muslin cloth and allowed to rest for 2 h at room temperature. The dough is then divided into small balls that are rolled into Chapati of desired diameter and thickness. The rolled dough is then baked on a hot plate until it attains light brown color on both sides.

Roti. Like Chapati it is also a round unleavened flat bread and is invariably prepared from whole-wheat flour. The whole-wheat flour dough after being kept for 2 h is divided into small balls that are then rolled as before for Chapati and stuck to the walls of previously heated dome-shaped earthen oven for baking. The baking time is 2–3 min. The heating material is wood, charcoal, or gas, and the temperature of the oven is about 550–600 °F.

Nan. It is a round leavened flat bread and is prepared from white flour known as Maida. The composition of Maida is included in Table I. The dough is made in the presence of salt and sodium bicarbonate (0.5%), covered with warm moist muslin cloth, and allowed to rest for about 2 h. The rest of the process is the same as for Roti.

Puri. The dough is made from white flour, i.e. Maida, in the presence of small quantities of salt and divided into small balls of about 40–50 g each. These are covered with a moist muslin cloth for about 1 h. Each ball is then rolled into thin circular shape. Puri of desired diameter is fried in hot edible oil to light brown or brown color. The frying time is about 15–30 s.

Roasted Wheat. The cleaned wheat is roasted in sand bath to light brown color until peculiar roasted wheat flavor is developed. Sand is then removed by sieving.

Dalya or Wheat Porridge. The roasted wheat is coarsely ground and fried in desired amount of edible fat for a short time. Water and sugar and/or salt are added and cooked into a porridge of desired thickness.

Whole-Wheat Flour (Chakki Ata). Wheat was purchased from the market, cleaned, and ground in a stone mill known as Chakki. In this type of mill the whole-wheat grain is ground to coarse flour that includes all parts of the whole seed.

Commercial wheat flour known as Ata is the coarse product obtained by roller milling cleaned and conditioned wheat and sieving it.

Maida is the fine product made by milling cleaned wheat and bolting the resulting wheat flour.

The composition of whole-wheat flour, commercial wheat flour, and Maida is given in Table I.

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