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Synthesis and Antiinflammatory Activity of Trisubstituted Pyrimidines and Triazines

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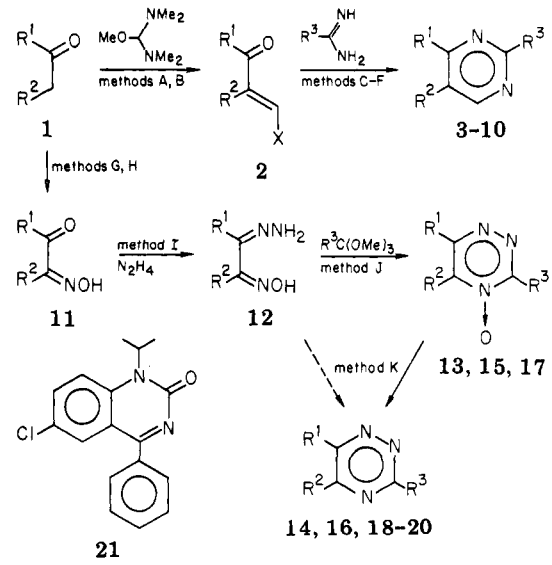
A series of mono-, bi-, and tricyclic pyrimidines and *as*-triazines was prepared and their antiinflammatory activity measured against carrageenan-induced edema in the rat. The more active analogues (ED_{50}), including 4-pyridylpyrimidines **4a** (38), **4b** (47), and **4g** (49) and 2-hydroxypyrimidine **8r** (43), were then tested against adjuvant-induced edema in the rat. None was active in the adjuvant arthritis model.

The search for new classes of nonsteroidal antiinflammatory agents which minimize gastrointestinal toxicity has led to a number of clinical candidates,[1-3] including the nonacidic heterocycle, proquazone (**21**).[3a,25] Despite these agents the need for more effective antirheumatic drugs continues to grow. To this end, a series of mono-, bi-, and tricyclic pyrimidines and *as*-triazines has been prepared and tested for antiinflammatory activity. A description of the synthesis of these compounds as well as a description of the structure–activity relationships is presented in this paper.

Chemistry. Chemically, our aim was to construct both the pyrimidine and triazine ring systems from common ketone precursors. Of the methods available,[4] those outlined in Scheme I were selected due to their general applicability to a variety of commercially available ketone systems as well as the simple nature of the reactions. Pyrimidine construction was accomplished by aminoformylation of an active methylene ketone **1** with Bredereck's reagent,[5] followed by cyclization of the resulting protected β-ketoaldehyde **2** [X = $N(CH_3)_2$] with an amidine equivalent. In some cases the ketones were formylated under standard conditions[6] with the resulting β-ketoaldehyde **2** (X = OH) converted into the corresponding enol ether **2** (X = OCH_2CH_3)[7] prior to cyclization. The cyclization with an amidine equivalent was, in general, most successful when performed in the presence of an equivalent of sodium ethoxide rather than under neutral or acidic conditions. Derivatization of the 2-amino- and

Scheme I



2-chloropyrimidines provided additional analogues (Table I).

The regiospecific preparation of *as*-triazines from the same α-methylene ketones **1** was accomplished by α-nitrosation, reaction of the resulting α-keto oxime **11** with hydrazine to form an α-hydrazino oxime **12**, and subsequent exposure under nonequilibrating conditions to an

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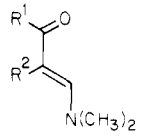
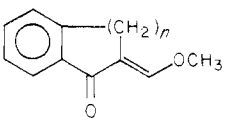
Table I. Protected β-Ketoaldehydes 2



2a-l

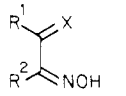


2m-o

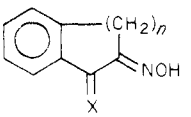
Compd	Mp or bp (mm), °C	Yield (%), method	R^1	R^2	n	Emp formula	Analyses
2a	70-72	95, A	C_6H_5	CH_3		$C_{12}H_{15}NO$	C, H, N
2b	115-117	96, A	4-C_5H_4N	H		$C_{10}H_{12}N_2O$	C, H, N
2c	62-70	74, A	3-C_5H_4N	H		$C_{10}H_{12}N_2O$	C, H, N
2d	125-127	79, A	2-C_5H_4N	H		$C_{10}H_{12}N_2O$	C, H, N
2e	Oil	67, A	4-C_5H_4N	CH_3		$C_{11}H_{14}N_2O$	C, H, N
2f	150-160 (0.1)	60, A	4-C_5H_4N	C_6H_5		$C_{16}H_{16}N_2O$	C, H, N
2g	135-142 (0.1)	82, A	$-(CH_2)_2CH(t\text{-Bu})CH_2-$			$C_{13}H_{22}NO$	C, H, N
2h	110-120 (0.10)	68, A	$-(CH_2)_2N(CH_3)CH_2-$			$C_9H_{16}N_2O$	C, H, N
2i	119-120	82, A	p-$CH_3OC_6H_4$	p-$CH_3OC_6H_4$		$C_{19}H_{21}NO_3$	C, H, N
2j	54.5-55.5	78, A	t-Bu	C_6H_5		$C_{15}H_{21}NO$	C, H, N
2k	68-73 (0.1)	63, A	t-Bu	H		$C_9H_{17}NO$	C, H, N
2l	98-105 (0.1)	75, A	$-(CH_2)_{10}-$			$C_{15}H_{27}NO$	C, H, N
2m	90-92[a]	73, B			1	$C_{11}H_{10}O_2$	C, H
2n	135-143 (0.75)[a]	58, B			2	$C_{12}H_{12}O_2$	C, H
2o	120-125 (0.05)[a]	57, B			3	$C_{13}H_{14}O_2$	C, H

[a] See ref 24.

Table II. Keto Oximes 11 and Hydrazino Oximes 12



11a-c, X = O
12a-c, X = NNH_2



11d,e, X = O
12d,e, X = NNH_2

Compd	Mp or bp (mm), °C	Yield (%), method	n	R^1	R^2	Emp formula	Analyses
11a	153-156	79, H		$-CH_2CH_2CH(t\text{-Bu})CH_2-$		$C_{10}H_{17}NO_2$	C, H, N
11b	113-115	68, G		C_6H_5	CH_3	$C_9H_9NO_2$	C, H, N
11c[a]	Oil	63		t-Bu	H	$C_6H_{11}NO_2$	C, H, N
11d	164 dec	80, G	1			$C_{10}H_9NO_2$	C, H, N
11e	126-127 dec	23, G	2			$C_{11}H_{11}NO_2$	C, H, N
12a	165-168 dec	90, I		$-CH_2CH_2CH(t\text{-Bu})CH_2-$		$C_{10}H_{19}N_3O$	C, H, N
12b	168-174	65, I		C_6H_5	CH_3	$C_9H_{11}N_3O$	C, H, N
12c	120-122	81, I		t-Bu	H	$C_6H_{13}N_3O$	C, H, N
12d	140-141 dec	85, I	1			$C_{10}H_{11}N_3O$	C, H, N
12e	174-175 dec	84, I	2			$C_{11}H_{13}N_3O$	C, H, N

[a] See ref 17.

appropriately substituted orthoester[8] (Table II). Continuous fractional distillation of any alcohol evolved during the ring formation step ensured nonequilibrating conditions. The fully aromatized triazines **20a–d** apparently result from intramolecular disproportionation (redox) of the expected dihydro *N*-oxides.

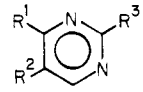
Pharmacology. The *as*-triazines and pyrimidines were tested for antiinflammatory activity against carrageenan-induced edema in the rat,[9] a screen which produces a large number of false positive responses.[10] To each group of five animals with the exception of the control group, drug was administered orally at a dose of 100 mg/kg of body weight, with one group receiving phenylbutazone at a dose of 25 mg/kg as a standard. One hour after drug treatment carrageenan (0.1 mL) was administered to the right hind paw of all animals (including the control group). After an additional 3–3.5 h the left and right hind paw volumes of all animals were measured. The percent reduction in paw volume was calculated by subtracting the difference between right and left hind paw volumes in the drug-treated group from the difference in the control group and dividing by the difference in the control group. The parenthesized values found in Tables III–V are the average percent reduction from two groups of five animals. The dashes indicate a reduction of <5%.

When a reduction in paw size of treated animals vs. controls greater than 50% was achieved, an ED_{50} or dose that causes a 50% reduction of the edema was calculated using the percent reduction values received at doses of 100, 50, 25, and 12.5 mg/kg. In this screen our standard phenylbutazone has an ED_{50} = 25 mg/kg while proquazone (**21**)[3a,25] displays an ED_{50} = 5.2 mg/kg. The ED_{50} values in Tables III–V are the nonparenthesized numbers. The more active analogues (ED_{50} < 50 mg/kg) were tested against adjuvant-induced edema in the rat at 30 mg/kg per os, a more specific model of chronic arthritis.[11]

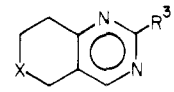
Discussion

The most active *as*-triazines (Table V) were 3-H substituted (**15a** and **17c**). In general, the 4-*N*-oxides were equal to or slightly more potent than the corresponding N compounds (**13a** > **14a**, **13b** = **14b**, **15a** > **16a**, **17a** =

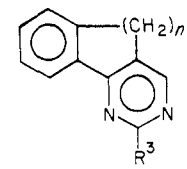
Table III. Pyrimidines 3-6 and 10



3a-c, 4a-p



5a-c, X = CH-*t*-Bu
6a-c, X = NCH_3



10a-c, $n = 2$
10d, $n = 3$
10e, $n = 1$

Compd	Mp or bp (mm), °C	Yield (%), method	R^1	R^2	R^3	Emp formula	Analyses	Carrageenan foot edema, ED_{50} (%)[c]
3a	181-182.5[b]	73, C	C_6H_5	CH_3	NH_2	$C_{11}H_{11}N_3$	C, H, N	(34)
3b	205-209[b]	59, C	C_6H_5	CH_3	CH_3	$C_{12}H_{12}N_2$	C, H, N	(12)
3c	100-105 (0.1)	70, C	C_6H_5	CH_3	H	$C_{11}H_{10}N_2$	C, H, N	(48)
4a	188.5-189	73, C	4-Pyridyl	H	NH_2	$C_9H_8N_4$	C, H, N	38
4b	65-68	61, C	4-Pyridyl	H	CH_3	$C_{10}H_9N_3$	C, H, N	47
4c	132-133.5	43, C	4-Pyridyl	H	H	$C_9H_7N_3$	C, H, N	(45)
4d	136.5-138	43, C	2-Pyridyl	H	NH_2	$C_9H_8N_4$	C, H, N	(17)
4e	186-188	53, C	3-Pyridyl	H	NH_2	$C_9H_8N_4$	C, H, N	(32)
4f	211-213 dec	67, C	4-Pyridyl	H	NHCN	$C_{10}H_7N_5$	C, H, N	–
4g	116.5-117.5	59, C	4-Pyridyl	H	$NHCH_3$	$C_{10}H_{10}N_4$	C, H, N	49
4h	235-236 dec	65, D	4-Pyridyl	H	$NHCOCH_3$	$C_{11}H_{10}N_4O$	C, H, N	(52)
4i	214-215	31, D	4-Pyridyl	H	$NHCO_2CH_2CH_3$	$C_{12}H_{12}N_4O_2$	C, H, N	(31)
4j	243-244	98, D	4-Pyridyl	H	$NH_2 \cdot CH_3I$	$C_{10}H_{11}N_4I$	C, H, N	(18)
4k	237-238.5 dec	42, D	4-Pyridyl	H	$NHCONH_2$	$C_{10}H_9N_5O$	C, H, N	(12)
4l	86-88	52, C	4-Pyridyl	H	C_6H_5	$C_{15}H_{11}N_3$	C, H, N	(42)
4m	235-236	52, C	4-Pyridyl	C_6H_5	NH_2	$C_{15}H_{12}N_4$	C, H, N	(48)
4n	153.5-155	37, C	4-Pyridyl	C_6H_5	H	$C_{15}H_{11}N_3$	C, H, N	95
4o	92-94	68, C	4-Pyridyl	CH_3	H	$C_{10}H_9N_3$	C, H, N	(50)
4p	234-235.5	72, C	4-Pyridyl	CH_3	NH_2	$C_{10}H_{10}N_4$	C, H, N	66
5a	202-203.5	34, C			NH_2	$C_{12}H_{19}N_3$	C, H, N	(41)
5b	95-100 (0.1)	77, C			H	$C_{12}H_{18}N_2$	C, H, N	58
5c	75-85 (0.1)	86, C			CH_3	$C_{13}H_{20}N_2$	C, H, N	–
6a	72-74	71, C			CH_3	$C_9H_{13}N_3$	C, H, N	(45)
6b	211-213	31, C			NH_2	$C_8H_{12}N_4$	C, H, N	–
6c	75-80 (0.1)	60, C			H	$C_8H_{11}N_3$	C, H, N	(50)
10a	225-225.5[a]	47, C			CH_3	$C_{13}H_{13}N_2Cl$	C, H, N, Cl	–
10b	245-246	75, C			NH_2	$C_{12}H_{11}N_3$	C, H, N	(32)
10c	218-220[a]	57, C			H	$C_{12}H_{11}N_2Cl$	C, H, N, Cl	(32)
10d	231-233[a]	61, C			CH_3	$C_{14}H_{15}N_2Cl$	C, H, N, Cl	–
10e	232-233[a]	50, C			CH_3	$C_{12}H_{11}N_2Cl$	C, H, N, Cl	–

[a] HCl Salt. [b] See ref 21. [c] Parenthesized numbers indicate a percent reduction. Dashes (–) indicate a reduction <5%.

18a, 17b = 18b). The 3-aryl-substituted *as*-triazines were considerably less potent than the 3-H analogues[12] (**13b > 13c, 17c > 17a**).

The 2-NH_2 (**4a**), 2-CH_3 (**4b**), and 2-$NHCH_3$ (**4g**) compounds were the most active analogues in the 4′-pyridylpyrimidine series (**4a–p**, Table III). One notices the potency trend 4′-pyridyl > 3′-pyridyl > 2′-pyridyl (**4a > 4e > 4d**). Addition of a methyl moiety at C-5 had an unpredictable effect on activity (**4a** vs. **4p** and **4c** vs. **4o**).

A phenyl moiety at C-5 enhanced potency when R^3 = H (**4c < 4n**) but reduced activity when $R^3 = NH_2$ (**4a > 4m**). The two cases in which a C-5 phenyl group was added in the C-4 *t*-Bu series and a comparison was possible (**8a** vs. **8p** and **8j** vs. **8x**) showed slight increases in potency over the 5-H compounds. The 2-OH compound **8r** was the most potent (ED_{50} = 43 mg/kg) member of the C-4 *t*-Bu series. In the case of the 4-*tert*-butyl-5-phenylpyrimidines **8a–o**, the 2-dimethylaminoacetyl analogue **8n** was most potent. The potency trend 2-H > 2-NH_2 > 2-Me was observed in the series **3c > 3a > 3b**, **5b > 5a > 5c**, **8c > 8a > 8b**, and **10c = 10b > 10a**.

None of the compounds tested against adjuvant-induced edema in the rat displayed a level of activity sufficient to warrant further investigation. Based on additional testing it would appear that these compounds represent a series of false positives in the carrageenan-induced edema model.

Experimental Section

General Comments. The IR spectra were recorded on a Perkin-Elmer 257 or 457 spectrometer and ^1H NMR spectra were recorded using either a Varian T-60 or A-60A spectrometer. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

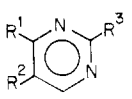
Silica gel (0.063–0.2 mm) was used in preparing column chromatograms and analytical thin-layer chromatography was conducted on precoated 40 × 80 mm plastic sheets of silica gel G with fluorescent indicator. In all workup procedures the drying process involved swirling over anhydrous magnesium sulfate and filtering prior to evaporation.

All new structures were assigned on the basis of spectral data and combustion analysis. The analyses are within 0.4%. No yields were optimized and all are reported as isolated yields.

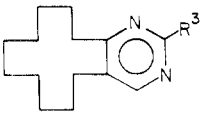
Method A. Preparation of α-Dimethylamino Methylene Ketones 2 [X = $N(CH_3)_2$]. The ketones 1 were aminoformylated according to literature procedures[5,13] with the results for compound **2a–e** summarized in Table I.

Method B. Preparation of α-Methoxymethylene Ketones 2 (X = OCH_3). The known enol ethers **2m–o**[24] (X = OCH_3) were prepared by standard formylation[6] and enol ether[7] procedures (Table I).

Table IV. Pyrimidines 7-9



7a,b, R^1 = *p*-$CH_3OC_6H_4$
8a-z, R^1 = *t*-Bu

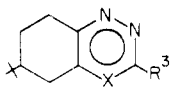


9a-c

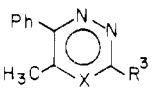
Compd	Mp or bp (mm), °C	Yield (%), method	R^2	R^3	Emp formula	Analyses	Carrageenan foot edema, ED_{50} (%)
7a	198-200	72, C	4-$CH_3OC_6H_4$	NH_2	$C_{18}H_{17}N_3O_2$	C, H, N	85
7b	93-97	56, C	4-$CH_3OC_6H_4$	CH_3	$C_{19}H_{18}N_2O_2$	C, H, N	–
8a	124.5-125.5	31, C	C_6H_5	NH_2	$C_{14}H_{17}N_3$	C, H, N	(46)
8b	85-90 (0.1)	94, C	C_6H_5	CH_3	$C_{15}H_{18}N_2$	C, H, N	(22)
8c	115-120 (0.5)	30, C	C_6H_5	H	$C_{14}H_{16}N_2$	C, H, N	(48)
8d	96-97	59, C	C_6H_5	C_6H_5	$C_{20}H_{20}N_2$	C, H, N	–
8e	152-153.5	33, C	C_6H_5	NHCN	$C_{15}H_{16}N_4$	C, H, N	–
8f	121.5-122.5	11, D	C_6H_5	$N(COCH_3)_2$	$C_{18}H_{21}N_3O_2$	C, H, N	(22)
8g	179-180.5	15, D	C_6H_5	$NHCO_2CH_2CH_3$	$C_{17}H_{21}N_3O_2$	C, H, N	(24)
8h	244-245.5	41, D	C_6H_5	$NHCONH_2$	$C_{15}H_{18}N_4O$	C, H, N	(14)
8i	105-108	43, D	C_6H_5	$NHCOCH_3$	$C_{16}H_{19}N_3$	C, H, N	(29)
8j	119.5-124	94, C	C_6H_5	$NHCH_3$	$C_{15}H_{19}N_3$	C, H, N	(37)
8k	250-251	54, C	C_6H_5	$NHNH_2$	$C_{14}H_{18}N_4$	C, H, N	–
8l	149.5-150.5	44, C	4-ClC_6H_4	NH_2	$C_{14}H_{16}N_3Cl$	C, H, N, Cl	(25)
8m	143.5-144.5	30, C	3-$F_3CC_6H_4$	NH_2	$C_{15}H_{16}N_3F_3$	C, H, N	(8)
8n	126-128	39, D	C_6H_5	$NHCOCH_2N(CH_3)_2$	$C_{18}H_{24}N_4O$	C, H, N	84
8o	189.5-191.5	59, D	C_6H_5	$NHCO(CH_2)_3COOH$	$C_{19}H_{23}N_3O_3$	C, H, N	(5)
8p	102.5-104	50, C	H	NH_2	$C_8H_{13}N_3$	C, H, N	(32)
8q	110.5-112	64, E	H	NHC_6H_5	$C_{14}H_{17}N_3$	C, H, N	(21)
8r	194-195[b]	53, F	H	OH	$C_8H_{12}N_2O$	C, H, N	43
8s	70-75 (0.1)	47, F	H	Cl	$C_8H_{11}N_2Cl$	C, H, N, Cl	–
8t	105-107	54, E	H	$NHCH_2C_6H_5$	$C_{15}H_{19}N_3$	C, H, N	(14)
8u	90.5-191.5[a]	66, E	H	$NHCH_2CH_2C_6H_5$	$C_{16}H_{22}N_3Cl$	C, H, N, Cl	(10)
8v	70-73	67, E	H	NH-*t*-Bu	$C_{12}H_{21}N_3$	C, H, N	(26)
8w	50-55 (0.1)	42, C	H	$N(CH_3)_2$	$C_{10}H_{17}N_3$	C, H, N	(18)
8x	48-51 (0.2)	52, C	H	$NHCH_3$	$C_9H_{15}N_3$	C, H, N	(34)
8y	170-171.5	65, E	H	SH	$C_8H_{12}N_2S$	C, H, N, S	(22)
8z	70-80 (0.5)	77, D	H	SCH_3	$C_9H_{14}N_2S$	C, H, N, S	(35)
9a	198-200	35, C		NH_2	$C_{14}H_{23}N_3$	C, H, N	–
9b	85-92 (0.1)	37, C		H	$C_{14}H_{22}N_2$	C, H, N	–
9c	128-135 (0.1)	57, C		CH_3	$C_{15}H_{24}N_2$	C, H, N	–

[a] HCl salt, hydrate. [b] See ref 22.

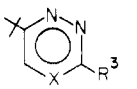
Table V. *as*-Triazines 13-20



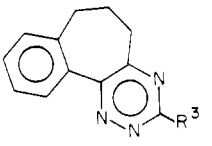
13a-c, X = N→O
14a,b, X = N



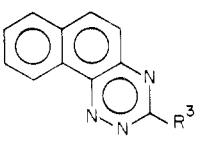
15a, X = N→O
16a,b, X = N



17a-c, X = N→O
18a,b, X = N



19a



20a-d

Compd	Mp or bp (mm), °C	Yield (%), method	R^3	Emp formula	Analyses	Carrageenan foot edema, ED_{50} (%)
13a	99-100	72, J	CH_3	$C_{12}H_{19}N_3O$	C, H, N	(48)
13b	129.5-131	51, J	H	$C_{11}H_{17}N_3O$	C, H, N	(36)
13c	123-125	27, J	C_6H_5	$C_{17}H_{21}N_3O$	C, H, N	(15)
14a	44.5-45.5	54, K	CH_3	$C_{12}H_{19}N_3$	C, H, N	–
14b	108.5-110	81, K	H	$C_{11}H_{17}N_3$	C, H, N	(49)
15a	122-126[a]	48, J	H	$C_{10}H_9N_3O$	C, H, N	64
16a	66-68[b]	56, K	H	$C_{10}H_9N_3$	C, H, N	–
16b	121-124[b]	37, K	C_6H_5	$C_{16}H_{13}N_3$	C, H, N	–
17a	145-146	43, J	C_6H_5	$C_{13}H_{15}N_3O$	C, H, N	(35)
17b	126-127	65, J	CH_3	$C_8H_{13}N_3O$	C, H, N	(22)
17c	133-134	59, J	H	$C_7H_{11}N_3O$	C, H, N	98
18a	73.5-74	84, K	C_6H_5	$C_{13}H_{15}N_3$	C, H, N	(38)
18b	51.5-52.5	98, K	CH_3	$C_8H_{13}N_3$	C, H, N	(25)
19a	80-82	49, K	H	$C_{12}H_{11}N_3$	C, H, N	–
20a	122-123	58, J	H	$C_{11}H_7N_3$	C, H, N	–
20b	95-96	52, J	CH_3	$C_{12}H_9N_3$	C, H, N	–
20c	135-145 (0.1)	85, J	$(CH_2)_3CH_3$	$C_{15}H_{15}N_3$	C, H, N	–
20d	117-118	35, J	C_6H_5	$C_{17}H_{11}N_3$	C, H, N	–

[a] See ref 23. [b] See ref 8.

Method C. Preparation of Pyrimidines 3–10 with Amidines. To a solution prepared by dissolving Na (0.69 g, 30 mmol) in absolute EtOH (200 mL) was added guanidine hydrochloride (2.86 g, 30 mmol). After stirring for 0.5 h at ambient temperature, a solution of 2-methyl-3-dimethylaminoacrylophenone (**2a**) (5.65 g, 30 mmol) in EtOH (20 mL) was added and the resulting mixture was heated at reflux for 8 h under N_2. The solution was then cooled and evaporated to dryness and the resulting residue partitioned between Et_2O and H_2O. Drying and evaporation of the Et_2O layer gave a solid which on recrystallization from EtOH gave 4.05 g (73%) of 2-amino-4-phenyl-5-methylpyrimidine (**3a**), mp 181–182.5 °C, as white needles.

In a similar manner, pyrimidines **3b,c**, **4a–g,l–p**, **5a–c**, **6a–c**, **7a,b**, **8a–e,j–m,w,x**, **9a–c**, and **10a–e** were prepared (Tables III and IV).

Method D. Alkylation/Acylation of the 2-Aminopyrimidines 3–10. A solution of 2-amino-4-(4-pyridyl)pyrimidine (**4a**) (3.10 g, 18 mmol) in Ac_2O (40 mL) was heated at reflux under N_2 for 3 h. After removal of the solvent in vacuo, the residue was partitioned between Et_2O and $NaHCO_3$. The organic layer was dried, the Et_2O evaporated, and the solid recrystallized from $CHCl_3$–MeOH to give 2.5 g (65%) of 2-acetamido-4-(4-pyridyl)pyrimidine (**4h**), mp 235–236 °C dec, as tan needles.

Acetylation of **8a** gave both the mono- (**8i**) and diacetylated (**8f**) products. Analogues **4i** and **8g** were prepared by reacting the corresponding aminopyrimidines **4a** and **8a** with ethyl chloroformate. Compound **4j** results from the quaternization of **4a** with MeI. While a single compound, it is unclear which N has undergone methylation. Ureas **4k** and **8h** are the hydrolysis products of the corresponding N–CN compounds **4f** and **8e**, respectively. Acylation of aminopyrimidine **8a** with chloroacetyl chloride followed by treatment with $HN(CH_3)_2$ provided **8n**, while acylation with glutaric anhydride gave **8o**. The thiomethyl analogue **8z** resulted from the alkylation of thiol **8y** with dimethyl sulfate.

Method E. Reactions of 2-Chloropyrimidine (8s). A mixture of 2-chloro-4-*tert*-butylpyrimidine (**8s**) (4.27 g, 25 mmol) in benzylamine (50 mL) was heated at reflux under N_2 for 18 h. Evaporation of the excess amine in vacuo, followed by partition of the residue between Et_2O and H_2O, drying, and evaporation, gave on recrystallization of the resulting solid from Et_2O 3.36 g (54%) of 2-benzylamino-4-*tert*-butylpyrimidine (**8t**) as a white solid, mp 105–107 °C.

Amines **8q,u,v** were prepared in a similar manner from **8s** and the appropriate amine. Thiol **8y** was prepared by reacting **8s** with thiourea rather than an amine.

Method F.[14] **Diazotization of 2-Aminopyrimidine (8p).** To a solution of concentrated HCl (10 mL) at 0 °C was added portionwise 2-amino-4-*tert*-butylpyrimidine (**8p**) (2.27 g, 10 mmol). While maintaining the reaction temperature below −10 °C, a solution of $NaNO_2$ (1.3 g) dissolved in 5 mL of H_2O was added dropwise and the resulting mixture was stirred for 1 h at −10 °C. After the pH was adjusted to 7, the mixture was allowed to warm to ambient temperature and extracted with $CHCl_3$. Chromatography of the $CHCl_3$ fraction over silica gel (175 g) afforded as a clear oil 2-chloro-4-*tert*-butylpyrimidine (**8s**) (0.81 g, 53%). Further elution with 10% MeOH–$CHCl_3$ provided 0.8 g (47%) of 2-hydroxy-4-*tert*-butylpyrimidine (**8r**), mp 194–195 °C.

Method G.[15] **4-*tert*-Butylcyclohexane-1,2-dione 2-Oxime (11a).** A solution of 4-*tert*-butylcyclohexanone (15.4 g, 0.1 mol) in Et_2O (150 mL) was saturated with HCl gas and to the resulting solution cooled to −50 °C was slowly added a solution of NOCl (4.25 g, 0.065 mol) in dry Et_2O (20 mL). After an additional 10 min at −50 °C the excess HCl was removed at −10 °C by passing a stream of N_2 through the solution, and the solution was quenched with 30% NaOH. The organic layer was removed, washed thoroughly with brine solution, dried, and evaporated to give, on trituration with petroleum ether, 9.4 g (79%) of 4-*tert*-butylcyclohexane-1,2-dione 2-oxime (**11a**), mp 153–156 °C, as a white solid.

Method H.[16] **1-Phenyl-1,2-propanedione 2-Oxime (11b).** To a saturated HCl solution of propiophenone (271.0 g, 2 mol) in Et_2O (2 L) at ambient temperature was added dropwise freshly distilled *n*-BuONO (226 mL, 2.00 mol), during which time a continuous stream of HCl gas was passed through the solution. The resulting mixture was stirred for 18 h and the solvent removed in vacuo. Recrystallization of the resulting residue from pentane–CH_2Cl_2 gave 222.1 g (68%) of 1-phenyl-1,2-propanedione 2-oxime (**11b**) as white needles, mp 113–115 °C.

Keto oxime **11c** was prepared according to the literature procedure.[17] Keto oximes **11d** and **11e** were prepared using the KOEt-catalyzed procedure of Zymalkowski[18] (Table II).

Method I.[8] **4-*tert*-Butylcyclohexane-1,2-dione 1-Hydrazone 2-Oxime (12a).** A solution of 4-*tert*-butylcyclohexane-1,2-dione 2-oxime (**11a**) (16.3 g, 0.1 mol) and hydrazine (3.16 mL, 0.1 mol) in absolute EtOH (100 mL) was heated under reflux for 20 h. After evaporation of the solvent the residue was dissolved in THF–Et_2O, washed with H_2O, dried, and evaporated. Trituration of this residue with CH_2Cl_2 gave 15.9 g (90%) of 4-*tert*-butylcyclohexane-1,2-dione 1-hydrazone 2-oxime (**12a**) as white needles, mp 165–168 °C dec.

Hydrazino oximes **12b–e** were prepared in a similar manner (Table II).

Method J.[8] **6-*tert*-Butyl-3-methyl-5,6,7,8-tetrahydro-1,2,4-benzotriazine 4-Oxide (13a).** Using a variable takeoff condenser to remove any MeOH formed during the reaction, a solution of 4-*tert*-butylcyclohexane-1,2-dione 1-hydrazone 2-oxime (9.85 g, 50 mmol) in trimethyl orthoacetate (35 mL) was heated at a bath temperature of 130 °C for 20 h. Evaporation of the solvent left a residue which on trituration with cold Et_2O gave 7.95 g (72%) of the benzotriazine **13a** as white crystals, mp 99–100 °C.

Using the same procedure the *as*-triazine 4-oxides **13b,c**, **15a**, and **17a–c** were also prepared. This procedure was also followed in the preparation of *as*-triazines **20a–d** (Table V).

Method K.[19] **6-*tert*-Butyl-3-methyl-5,6,7,8-tetrahydro-1,2,4-benzotriazine (14a).** A mixture of benzotriazine **13a** (2.21 g, 10 mmol), cyclohexene (3 mL), and 10% Pd/C (0.2 g) in EtOH (60 mL) was heated at reflux for 18 h under N_2. Filtration and evaporation of the filtrate produced a solid, which on crystallization from hexane gave 1.1 g (54%) of triazine **14a**, mp 44.5–45.5 °C. The $(EtO)_3P$ procedure of Burdon, while successful, proved less reliable.[20] Triazines **16a,b** were prepared in a similar manner (Table V).

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Aromatic Esters of Nonquaternary Carbon-4 Piperidinols as Analgesics[1]

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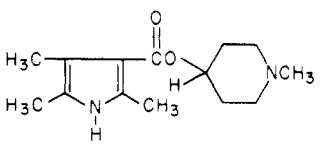
Aromatic carboxylic esters of 1-methyl-4-piperidinol were prepared and evaluated for analgesic activity. In addition, aralkyl, alkyl, and cycloalkyl carboxylates of the 4-piperidinol system and 3,4-dimethoxybenzoates of isomeric piperidinols (**24**–**26**) were synthesized. The 3,4-dimethoxybenzoate **23** was nearly twice as active as codeine in the mouse hot-plate assay. In monkeys, **23** showed no morphine-like physical dependence liability. *cis*- and *trans*-1,3-dimethyl-4-piperidinol esters **24** and **25** showed no binding to the opiate receptor in rat brain homogenates. The 3- and 4-monosubstituted and the 3,4-disubstituted benzoate esters were examined for qualitative structure–activity relationships with respect to parameters E_s^c and π. Various structural features of this series of compounds that may have an affinity for receptor binding sites are discussed.

Recent studies have shown that 1-methyl-4-piperidinol esters **1** and **2** and related structures possess analgesic activity and, in general, display no physical dependence liability of the morphine type in monkeys.[2,3] Furthermore, pyrrole ester **1** exhibits marginal affinity and piperonylate ester **2** virtually no affinity for the opiate receptor in rat brain homogenates.[3] Pethidine and alphaprodine, the well-known piperidine analgesics, have physical dependence and abuse liabilities. Structurally, **1** and **2** lack the



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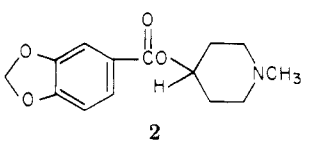

2

quaternary phenyl substitution at C-4 of the piperidine ring that is present in pethidine and alphaprodine.

From earlier studies,[2,3] it became apparent that either a heterocyclic or an aromatic ring could be interchanged in the acyl part of these structures, **1** and **2**, without any significant loss of activity. It was therefore of interest to extend the study of aromatic esters of the type similar to **2**. In this series, substituent effects were examined, since π, E_s^c, and/or σ parameters may influence their receptor interaction, passage through the blood–brain barrier, and metabolism. Consequently, ortho-, meta-, and para-substituted benzoic esters of 1-methyl-4-piperidinol were studied extensively (Table I). In addition, aralkyl (**27**, **40**–**43**), alkyl (**44**), and cycloalkyl (**45**) carboxylates of the 4-piperidinol system were synthesized in order to gain further insight into the aromatic ring involvement in receptor interactions. 3,4-Dimethoxybenzoates of *cis*- and *trans*-piperidinols (**24**–**26**) were prepared to determine if potency factors exist in stereoisomers of this type (Table II). Selected compounds were assayed for binding affinity to the opiate receptor (Results and Discussion). The esters were synthesized by three procedures as outlined in the Experimental Section.

Results and Discussion

The compounds were assayed for analgesic activity by the mouse hot-plate[4] and Nilsen methods[5] (Table II). The unsubstituted benzoate ester of 1-methyl-4-piperidinol (**3**) had an ED_{50} of 9.6 in the mouse hot-plate assay. In general, alkyl substitutions of the aromatic ring had a detrimental effect on activity, with the exception of the 2-methyl- and 2,4,6-trimethyl-substituted esters (**4**, ED_{50} = 8.9, and **13**, ED_{50} = 8.3, respectively). Ester **3** and the 2,6-dimethyl ester **9** were shown to have local anesthetic activity (see Table I for references). Compounds **33**–**38**, containing electron-withdrawing halogen groups, were all less active than the parent benzoate **3**. Compound **15** (ED_{50} = 16.6), having an electron-withdrawing hydroxyl group in the meta position, was one-half as potent as codeine. The methoxy-substituted benzoate esters of the nonstereospecific 1-methyl-4-piperidinol were the most active in this series. They displayed activity in the codeine range with the exception of the 2,6-dimethoxybenzoate **21**, which exhibited low activity (ED_{50} = 73.8) in the mouse hot-plate assay. Interestingly, the 2-methoxy derivative **16** showed an ED_{50} of 10.6, whereas the bulkier 2-ethoxy (**30**), 2-phenoxy (**31**), and 2-phenethyl (**32**) compounds were only marginally active. The 3-methoxybenzoate **17** showed an ED_{50} of 6.1 in the hot-plate assay, whereas the 3,4-dimethoxybenzoate **23**, the most active ester in this series, had an ED_{50} of 3.9 (hot-plate) (Chart I). It was nearly twice as active as codeine and 20% more active than pyrrole ester **1**. The piperonylate ester **2**, structurally related to **23**, was shown to have an ED_{50} of 7.3,[3] whereas the 3,4-dimethyl (**10**) and 3,4-dichloro (**37**), analogues of