Synthesis and Analgesic Activity of 1,3-Dihydro-3-(substituted phenyl)imidazo[4,5-*b*]pyridin-2-ones and 3-(Substituted phenyl)-1,2,3-triazolo[4,5-*b*]pyridines

Robert L. Clark, Arsenio A. Pessolano, Tsung-Ying Shen,* David P. Jacobus, Howard Jones,

Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065

Victor J. Lotti, and Lars M. Flataker

Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486. *Received June 13, 1977*

In a study of nonsteroidal antiinflammatory and analgesic agents, a series of 1,3-dihydro-3-(substituted phenyl)imidazo[4,5-*b*]pyridin-2-ones and 3-(substituted phenyl)triazolo[4,5-*b*]pyridines was prepared. Many of the imidazolones were alkylated on the free nitrogen. In a modified Randall–Selitto analgesic assay, the pain thresholds of both the inflamed and normal foot were elevated. This is not commonly observed with nonsteroidal antiinflammatory agents. The most active compounds were 1,3-dihydro-3-[3,4-(methylenedioxy)phenyl]imidazo[4,5-*b*]pyridin-2-one (I-15) and its *N*-allyl (I-21) and *N*-isopropyl (I-121) derivatives. In the triazole series the 3-(2-fluoro- and 2,4-difluorophenyl)triazolo[4,5-*b*]pyridines (T-1 and T-8) were the best. The imidazole compounds were somewhat superior in analgesic activity to codeine and *d*-propoxyphene without showing any narcotic characteristics. Some of the compounds also possessed activity against carrageenan-induced foot edema in the rat, so these compounds represent a new class of nonnarcotic analgesic antiinflammatories, capable of producing a greater degree of analgesia than that obtainable with other nonsteroidal antiinflammatory agents.

In our continuing study of nonacidic antiinflammatory agents[1] it was found that several 1,3-dihydro-3-(substituted phenyl)imidazo[4,5-*b*]pyridin-2-ones and 3-(substituted phenyl)triazolo[4,5-*b*]pyridines possessed interesting analgesic activity in a modified Randall–Selitto assay. The pain thresholds of both inflamed and normal feet were elevated. The analgetic effect on the normal foot is not commonly observed with nonsteroidal antiinflammatory agents, whose peripheral analgesic actions are usually limited to the inflamed foot only.[2] Since nonacidic antiinflammatory agents are generally less irritating in the gastrointestinal tract,[3] the potential utility of these two series of compounds was investigated.

Previously, a group of 1,3-dihydro-1-aminoalkyl-3-phenylimidazo[4,5-*b*]pyridin-2-ones was studied by Ciba Geigy[4] as antidepressant agents. 1,3-Dihydroimidazo-[4,5-*b*]pyridin-2-ones with substituents on the pyridine ring were reported by American Cyanamid,[5] Shell,[6] and Deutsche Gold and Silber Scheideanstalt[7] to possess antiphlogistic activity or have postemergence applications on broad leaved plants. A number of chemical investigations[8] have been made of the reaction of a 2,3-diaminopyridine and ethyl acetoacetate. One of the products is a 1,3-dihydroimidazo[4,5-*b*]pyridin-2-one. In the triazolopyridine series, 3-phenyl-5-chlorotriazolo-[4,5-*b*]pyridine was used by Glaxo[9] as an intermediate in the preparation of α-carbolines.

About 200 compounds in the two series were prepared and each compound was tested for its analgesic activity. Common intermediates can be used for both series. They are 2-(substituted phenylamino)-3-nitropyridines, **2**. These were prepared from the appropriate aniline and 2-chloro-3-nitropyridine. These reactions were carried out under various conditions. A mixture of 2-fluoroaniline and 2-chloro-3-nitropyridine reacted exothermally after it was warmed on a steam bath. Other reactants, such as 4-aminoacetanilide and 2-chloro-3-nitropyridine, required heating to 190 °C to initiate the reaction. Some reactions, such as 3,4-(methylenedioxy)aniline with 2-chloro-3-nitropyridine, were controlled better if the reactants were heated in acetic acid in the presence of sodium acetate. The vigorous reaction between 3,4-(methylenedioxy)aniline and 2-chloro-3,5-dinitropyridine was controlled by first diluting the aniline with methanol and then adding the 2-chloro-3,5-dinitropyridine at room temperature. The product crystallized almost immediately. In other cases the reactants were refluxed in pyridine or dimethylformamide. Other variations involved the use of 2-chloronitrobenzene or 2,4-dichloro-5-nitropyrimidine instead of 2-chloro-3-nitropyridine. These reacted similarly to the pyridine. A few benzylamines were used instead of aniline; they were especially reactive and the reactants needed to be diluted with a solvent such as benzene to control the reaction (Tables I–III).

Most of the nitro compounds, **2**, were catalytically hydrogenated to give the 2,3-diaminopyridines. In many cases this diamine, **3**, was unstable, so it was not characterized but immediately used in the next step. With a 3,5-dinitropyridine the 3-nitro group was reduced with hydrogen sulfide in an ammoniacal solution. Hydrogenation of the 2-chloro-5-nitropyrimidine removed the chlorine atom as well as reducing the nitro group.

The most convenient method of converting the diamine, **3**, to the imidazo[4,5-*b*]pyridin-2-one, **4**, was through reaction with phosgene. In some cases this was not satisfactory and the diamine was heated with urea to give the desired product. Potassium ethyl xanthate was used to give the corresponding thio compound, **7**.

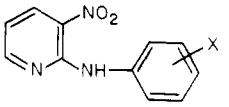
The free nitrogen of the imidazo[4,5-*b*]pyridin-2-one was alkylated with alkyl halide in refluxing acetone solution in the presence of powdered potassium hydroxide according to the method of Pachter and Kloetzel.[10] In the case of imidazo[4,5-*b*]pyridine-2-thione (I-24), the alkylation occurred on the sulfur and not on the nitrogen. Alkylation of I-15 with *tert*-butyl bromide gave low yields of a mixture of O- and N-alkylated products (I-130 and I-131). The chemical preparation of these compounds is depicted in Scheme I.

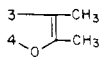
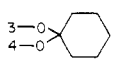
Discussion

The analgesic assay is essentially the one described by Winter and Flataker.[11a] One foot of a Sprague–Dawley female rat is made sensitive by an injection of brewer's yeast, and the response threshold was determined by applying pressure to each foot and reading on a manometer the pressure at which an audible "squeak" was elicited. For the initial evaluation, three rats are given an aqueous suspension of the compound orally by stomach tube at 32

0022-2623/78/1821-0965$01.00/0 © 1978 American Chemical Society

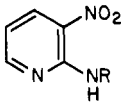
Table I. 2-Anilino-3-nitropyridines

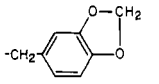
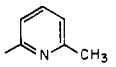


compd	X	yield, %	method	mp, °C	formula
N-1	2-F	50	A-180[a]	102-103	$C_{11}H_8FN_3O_2$
N-2	H		*b*		
N-3	4-MeO	80	A-180	78-80	$C_{12}H_{11}N_3O_3$
N-4	4-F	85	A-200	130-131	$C_{11}H_8FN_3O_2$
N-5	2-*i*-Pr	80	A-190	96-98	$C_{14}H_{15}N_3O_2$
N-6	2,6-Me_2	75	A-190	114-115	$C_{13}H_{13}N_3O_2$
N-7	3-CF_3	80	A-185	81-82	$C_{12}H_8F_3N_3O_2$
N-8	2,4-F_2	75	A-190	114-116	$C_{11}H_7F_2N_3O_2$
N-9	2-Cl	50	A-190	128-129	$C_{11}H_8ClN_3O_2$
N-10	2-Me_2N	40	A-165	*c*	$C_{13}H_{14}N_4O_2$
N-11	3-F	75	A-185	102-104	$C_{11}H_8FN_3O_2$
N-12	4-Et	85	A-180	83-84	$C_{13}H_{13}N_3O_2$
N-13	2-F,5-Me	75	A-200	114-117	$C_{12}H_{10}FN_3O_2$
N-14	4-Me		*b*		
N-15	3,4-OCH_2O-	92	*d*	146-148	$C_{12}H_9N_3O_4$
N-16	4-NHAc	45	A-190	176-177	$C_{13}H_{12}N_4O_3$
N-17	2,4-Me_2	70	A-175	121-125	$C_{13}H_{13}N_3O_2$
N-18	2,5-F_2	70	A-180	150-152	$C_{11}H_7F_2N_3O_2$
N-22	2-Br	40	A-185	138-140	$C_{11}H_8BrN_3O_2$
N-25	3,4-$O(CH_2)_2O$-	90	B	126-127	$C_{13}H_{11}N_3O_4$
N-26	2,4-Cl_2	80	A-185	144-145	$C_{11}H_7Cl_2N_3O_2$
N-27	2,6-F_2	25	A-190	*c*	$C_{11}H_7F_2N_3O_2$
N-28	4-Cl	55	A-190	145-147	$C_{11}H_8ClN_3O_2$
N-30	3,4-$(MeO)_2$	85	B	97-98	$C_{13}H_{13}N_3O_4$
N-43	2-Me,3-Cl	63	*d*	134-135	$C_{12}H_{10}ClN_3O_2$
N-47	3,4-Cl_2	90	A-180	167-168	$C_{11}H_7Cl_2N_3O_2$
N-49	3,4,5-$(MeO)_3$	90	B	139-140	$C_{14}H_{15}N_3O_5$
N-50	2,4-$(MeO)_2$	80	B	139-140	$C_{13}H_{13}N_3O_4$
N-59	4-C_6H_5O	75	A-100	105-107	$C_{17}H_{13}N_3O_3$
N-65	3,4-CH_2OCH_2-	65	B	146-147	$C_{13}H_{11}N_3O_3$
N-67	2-F[e]	31	*d*	159-161	$C_{11}H_7FN_4O_4$
N-68	3-MeO	65	A-175	98-100	$C_{12}H_{11}N_3O_3$
N-74	2,5-$(MeO)_2$	90	B	145-147	$C_{13}H_{13}N_3O_4$
N-77	3,4-Me_2	65	B	134-136	$C_{13}H_{13}N_3O_2$
N-81	3-C_6H_5O	55	A-185	81-82	$C_{17}H_{13}N_3O_3$
N-82	2-F[f]	50	A-190	114-115	$C_{12}H_{10}FN_3O_2$
N-85	3-MeO,4-Me	85	B	101-102	$C_{13}H_{13}N_3O_3$
N-88	3,4-$OC(CH_3)_2O$-	65	B	oil[c]	$C_{14}H_{13}N_3O_4$
N-90		75	A-155	114-116	$C_{15}H_{13}N_3O_3$
N-91	3,4-OCH_2O-,6-Me	65	B	167-168	$C_{13}H_{11}N_3O_4$
N-92	3,4-$(CH_2)_3$-	55	B	103-104	$C_{14}H_{13}N_3O_2$
N-95		90	B	117-118	$C_{17}H_{17}N_3O_4$
N-96	3,4-$OC(Et)_2O$-	70	B	95-96	$C_{16}H_{17}N_3O_4$
N-98	3,4-CH_2OCH_2O-	45	*g*	130-131	$C_{13}H_{11}N_3O_4$
N-100	3,4-$(CH_2)_4$-	40	B	116-118	$C_{15}H_{15}N_3O_2$
N-103	2,3-OCH_2O-	30	B	194	$C_{12}H_9N_3O_4$
N-105	4-COOH	55	A-172	292	$C_{12}H_9N_3O_4$
N-106	2-F[h]	45	*d*	145-148	$C_{13}H_{10}FN_3O_4$
N-107	3,4-OCH_2O-	50	A-100	196	$C_{14}H_{11}N_3O_6$[i]
N-110	3-COOEt	80	A-200	82-83	$C_{14}H_{13}N_3O_4$
N-138	4-CH_2COOH	25	*j*	169	$C_{13}H_{11}N_3O_4$
N-139	4-*i*-Bu	50	B	46-48	$C_{15}H_{17}N_3O_2$
N-140	2-MeO	55	B	151-152	$C_{12}H_{11}N_3O_3$
N-143	2-F[k]	20	A-160	107-109	$C_{11}H_7ClFN_3O_2$
N-144	3-CN	40	A-175	155-157	$C_{12}H_8N_4O_2$
N-145	4-Me_2N	70	A-170	137	$C_{13}H_{14}N_4O_2$
N-147	4-$COCH_3$	25	A-185	155-157	$C_{13}H_{11}N_3O_3$
N-149	4-Et	80	A-180	83-84	$C_{13}H_{13}N_3O_2$

[a] Refers to the maximum temperature (°C) attained in the preparation. [b] Reference 24. [c] Not purified. [d] Preparation given in the Experimental Section. [e] Also 5-nitro in pyridine ring. [f] Also 5-methyl in pyridine ring. [g] Reaction done in refluxing pyridine. [h] Also 5-carbomethoxy in pyridine ring. [i] C: calcd, 53.00; found, 52.54. [j] Reaction done in refluxing DMF. [k] Also 6-chloro in pyridine ring.

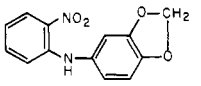
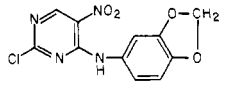
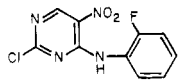
Table II. 2-Amino-3-nitropyridines



compd	R	yield, %	method	mp, °C	formula
N-23	$-CH_2CH_2C_6H_5$	75	A-130[a]	86-87	$C_{13}H_{13}N_3O_2$
N-31		32	*b*	113-115	$C_{13}H_{11}N_3O_4$
N-48	$-CH_2C_6H_4$-2-Fl	83	*b*	116-118	$C_{12}H_{10}FN_3O_2$
N-72	c-C_6H_{11}	65	A-80	oil[c]	$C_{11}H_{15}N_3O_2$
N-76		50	A-175	153-154	$C_{11}H_{10}N_4O_2$
N-141		30	A-185	165-167	$C_{10}H_8N_4O_2$

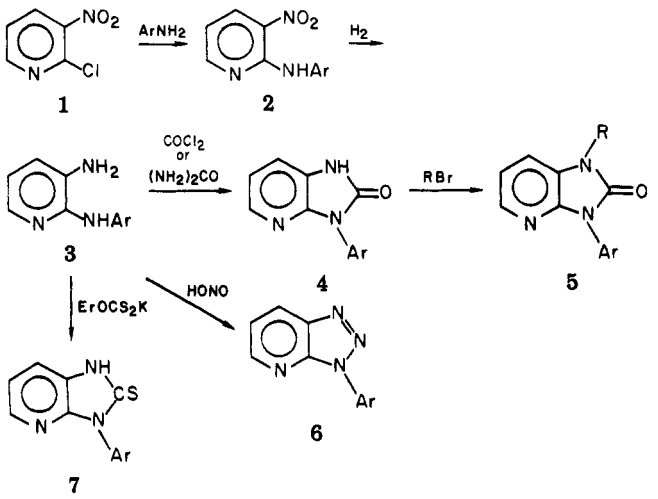
[a] Refers to the maximum temperature (°C) attained in the preparation. [b] Preparation given in the Experimental Section. [c] Not purified.

Table III. Miscellaneous Nitro Compounds

compd	structure	method	yield, %	mp, °C	formula
N-84		*a*	17	109-111	$C_{13}H_{10}N_2O_4$
N-120		*a*	73	143-145	$C_{11}H_7ClN_4O_4$[b]
N-133		*c*	40	147-148	$C_{10}H_6ClFN_4O_2$

[a] Preparation given in the Experimental Section. [b] C: calcd, 44.83; found, 45.47. [c] The two reagents were mixed in an ether solution at room temperature.

Scheme I



or 64 mg/kg. Tests with compounds that show activity are repeated using six rats per dose level. The results are shown in Tables IV–VIII.

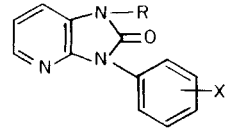
In this assay 1,3-dihydro-3-phenylimidazo[4,5-*b*]-pyridin-2-one (I-2) possessed activity of the order of codeine. The related 3-phenyltriazolopyridine (T-2) was less active, but in this triazole series the substitution of a 2-fluorophenyl for phenyl resulted in a compound (T-1) which also approached the activity of codeine. Many compounds in both series were prepared with electron-withdrawing and electron-donating substituents on the phenyl ring. Although many of these compounds showed modest activity, the 3,4-(methylenedioxy)phenyl group on the imidazopyridine seemed to give the most active compound (I-15). Surprisingly, the same group did not enhance the activity in the triazolopyridine series (T-15). Seemingly minor changes in the (methylenedioxy)phenyl group lowered or destroyed the activity. An ethylenedioxy group (I-25), or the substitution of dimethyl (I-88), diethyl (I-96), or pentamethylene (I-95), on the methylene carbon gave compounds devoid of activity. Similar groups such as 2,3-(methylenedioxy)phenyl (I-103), 3,4-(methylenedioxy)-6-methylphenyl (I-91), 3,4-dimethoxyphenyl (I-30), indanyl (I-92), or 1,2-dimethylbenzofuryl (I-90) also produced inactive compounds.

A few examples of other related structures were also prepared and tested for analgesic activity. Instead of using substituted anilines to give the 3-substituted phenyl derivatives, compounds such as 2-amino-6-methylpyridine (I-76), phenylethylamine (I-23), 3,4-(methylenedioxy)-benzylamine (I-31), and cyclohexylamine (I-72) were used, but these resulted in inactive compounds. Substituents on the pyridine ring, or replacement of it by a benzene or pyrimidine ring, also resulted in inactive compounds. The sulfur analogue of an active compound (I-24) was also inactive as well as a 2-phenylimidazopyridine (I-75).

Alkylation of the unsubstituted nitrogen sometimes yielded compounds with increased activity. The alkyl groups conferring the best activity were allyl, *n*-propyl, and isopropyl. The cyclopropylmethyl group, an activity enhancing group in many analgesics, did not help in this series.

An attempted "Hansch analysis" of most of the 1,3-dihydro-3-(substituted phenyl)imidazo[4,5-*b*]pyridin-2-

Table IV. 3-(Substituted phenyl)imidazo[4,5-*b*]pyridin-2-ones



compd	X	R	method	yield, %	mp, °C	formula	analgesic act. sensitive foot	analgesic act. normal foot
I-1	2-F	H	*a*	31	199–202	$C_{12}H_8FN_3O$	+[b]	–
I-2	H	H	D	30	240–241	$C_{12}H_9N_3O$	+++	+
I-3	4-MeO	H	D	30	257–258	$C_{13}H_{11}N_3O_2$	–	–
I-4	4-F	H	D	35	271–272	$C_{12}H_8FN_3O$	+	+
I-5	2-*i*-Pr	H	D	15	202–204	$C_{15}H_{15}N_3O$	–	–
I-6	2,6-Me_2	H	E	60	236–239	$C_{14}H_{13}N_3O$	+	–
I-7	3-CF_3	H	D	15	177–178	$C_{13}H_8F_3N_3O$	–	–
I-8	2,4-F_2	H	D	20	240–242	$C_{12}H_7F_2N_3O$	+	–
I-9	2-Cl	H	D	30	242–244	$C_{12}H_8ClN_3O$	++	–
I-10	2-Me_2N	H	D	25	222–224	$C_{14}H_{14}N_4O$	–	–
I-11	3-F	H	D	40	224	$C_{12}H_8FN_3O$	–	–
I-12	4-Et	H	D	60	214–215	$C_{14}H_{13}N_3O$	–	–
I-13	2-F,5-Me	H	D	45	206–208	$C_{13}H_{10}FN_3O$	–	+
I-14	4-Me	H	D	33	222–224	$C_{13}H_{11}N_3O$	++	++
I-15	3,4-OCH_2O-	H	*a*	30	259–260	$C_{13}H_9N_3O_3$	++++	++++
I-16	4-NH_2	H	D[c]	65	301	$C_{12}H_{10}N_4O$	++	–
I-17	2,4-Me_2	H	D	25	110–112	$C_{14}H_{13}N_3O \cdot 0.5H_2O$	++	–
I-18	2,5-F_2	H	D	65	229	$C_{12}H_7F_2N_3O$	–	–
I-19	3,4-OCH_2O-	Ac	H	70	211–212	$C_{15}H_{11}N_3O_4$	+	+
I-20	3,4-OCH_2O-	Me	F	85	238–239	$C_{14}H_{11}N_3O_3$	++	++++
I-21	3,4-OCH_2O-	$CH_2CH{=}CH_2$	*a*	69	130–131	$C_{16}H_{13}N_3O_3$	++++	++++
I-22	2-Br	H	D	35	240–243	$C_{12}H_8BrN_3O$[d]	+	–
I-25	3,4-$O(CH_2)_2O$-	H	D	35	267–269	$C_{14}H_{11}N_3O_3$	–	–
I-26	2,4-Cl_2	H	D	25	172–174	$C_{12}H_7Cl_2N_3O$	–	–
I-27	2,6-F_2	H	D	10	252–255	$C_{12}H_7F_2N_3O$	–	–
I-28	4-Cl	H	D	85	267–269	$C_{12}H_8ClN_3O$	–	–
I-29	3,4-OCH_2O-	$(CH_2)_2NEt_2$	F	50	172–173[e]	$C_{19}H_{22}N_4O_3 \cdot 2C_7H_8SO_3$	–	–
I-30	3,4-$(MeO)_2$	H	D	50	245–246	$C_{14}H_{13}N_3O_3$	–	–
I-32	2-F	$CH_2CH{=}CH_2$	F	65	92–94	$C_{15}H_{12}FN_3O$	+	–
I-33	3,4-OCH_2O-	$CH_2C{\equiv}CH_2$	F	40	207–209	$C_{16}H_{11}N_3O_3$	–	–
I-34	3,4-OCH_2O-	$CH_2C(CH_3){=}CH_2$	F	75	119–121	$C_{17}H_{15}N_3O_3$	–	–
I-35	3,4-OCH_2O-	SO_2CF_3	F	80	155–156	$C_{14}H_8F_3N_3O_5S$	–	–
I-36	3,4-OCH_2O-	*i*-Am	F	45	91–93	$C_{18}H_{19}N_3O_3$	–	–
I-37	3,4-OCH_2O-	$CH_2C_6H_5$	F	75	111–113	$C_{20}H_{15}N_3O_3$	–	–
I-38	3,4-OCH_2O-	$CH_2COOC_2H_5$	F	18	144–146	$C_{17}H_{15}N_3O_5$	–	–
I-39	3,4-OCH_2O-	$CH_2CCl{=}CH_2$	*a*	8	122–123	$C_{16}H_{12}ClN_3O_3$	++	++
I-40	3,4-OCH_2O-	$CH{=}C{=}CH_2$	*a*	15	195–196	$C_{16}H_{11}N_3O_3$	–	–
I-41	3,4-OCH_2O-	C(=O)-c-C_3H_5	F	45	192–193	$C_{17}H_{13}N_3O_4$	–	–
I-42	3,4-OCH_2O-	$CH_2CH{=}C(CH_3)_2$	F	75	109–110	$C_{18}H_{17}N_3O_3$	–	–
I-43	2-Me,3-Cl	H	D	15	224–225	$C_{13}H_{10}ClN_3O$	–	–
I-44	3,4-OCH_2O-	CH_2-c-C_3H_5	F	38	141–142	$C_{17}H_{15}N_3O_3$	++	++
I-45	3,4-OCH_2O-	*n*-Pr	*a*	80	112–114	$C_{16}H_{15}N_3O_3$	+++	++++

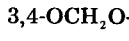
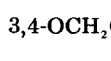
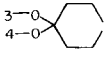
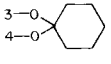
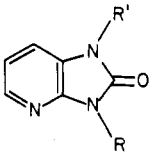
I-46	3,4-OCH_2O–	$(CH_2)_2C_6H_5$	F	40	123–124	$C_{21}H_{17}N_3O_3$	–	–
I-47	3,4-Cl_2	H	D	18	282	$C_{12}H_7Cl_2N_3O$	–	–
I-49	3,4,5-$(MeO)_3$	H	D	23	265–266	$C_{15}H_{15}N_3O_4$	–	–
I-50	2,4-$(MeO)_2$	H	D	72	204–206	$C_{14}H_{13}N_3O_3$	–	–
I-51	3,4-OCH_2O–	CH_2COOH	*a*	18	283	$C_{15}H_{11}N_3O_5 \cdot H_2O$	–	–
I-52	3,4-OCH_2O–		F	55	171–173	$C_{16}H_{13}N_3O_4$	–	–
I-53	3,4-OCH_2O–	$(CH_2)_3N(CH_3)_2$	F	13	97–99	$C_{18}H_{20}N_4O_3$	–	–
I-54	3,4-OCH_2O–		*a*	30	224–226	$C_{16}H_{12}N_4O_3S$	–	–
I-55	3,4-OCH_2O–	$CH_2CH{=}CHC_6H_5$	F	75	160–161	$C_{22}H_{17}N_3O_3$	–	–
I-56	3,4-OCH_2O–	$COOC_2H_5$	F	75	191–192	$C_{16}H_{13}N_3O_5$	–	–
I-57	3,4-OCH_2O–	$CH_2COC_6H_5$	F	80	79–81	$C_{21}H_{15}N_3O_4 \cdot (CH_3)_2CO$	–	+
I-58	3,4-OCH_2O–	CH_2OH	*a*	72	268	$C_{14}H_{11}N_3O_4$	++	+
I-59	4-C_6H_5O	H	D	30	236–237	$C_{18}H_{13}N_3O_2$	–	–
I-60	3,4-OCH_2O–	$(CH_2)_2OH$	F	25	194–196	$C_{15}H_{13}N_3O_4$	+++	++
I-61	3,4-OCH_2O–	$CH_2C(=O)$-c-$N(CH_2CH_2)_2O$	*a*	14	212–213	$C_{19}H_{18}N_4O_5$	–	–
I-63	3,4-OCH_2O–	$S(=O)_2C_6H_4$-4-F	F	70	144–145	$C_{19}H_{12}FN_3O_5S$	–	–
I-64	3,4-OCH_2O–	*i*-Bu	F	15	124–126	$C_{17}H_{17}N_3O_3$	++	–
I-65	3,4-CH_2OCH_2–	H	D	15	248–250	$C_{14}H_{11}N_3O_2$	–	–
I-66	2-F[f]	H	*g*	85	220–221	$C_{12}H_9FN_4O$	–	–
I-67	2-F[h]	H	E	40	234–236	$C_{12}H_7FN_4O_3$	–	–
I-68	3-MeO	H	D	50	196–198	$C_{13}H_{11}N_3O_2$	–	–
I-70	3,4-OCH_2O–	$(CH_2)C_6H_{11}$	F	70	103–104	$C_{21}H_{23}N_3O_3$	–	–
I-71	3,4-OCH_2O–	$CONHC_4H_9$	*a*	24	129–130	$C_{18}H_{18}N_4O_4$	–	–
I-74	2,5-$(MeO)_2$	H	D	55	243–244	$C_{14}H_{13}N_3O_3$	–	–
I-77	3,4-Me_2	H	D	63	188–190	$C_{14}H_{13}N_3O$	–	–
I-78	3,4-OCH_2O–	$(CH_2)_5CH_3$	F	68	65–66	$C_{19}H_{21}N_3O_3$	+	–
I-79	2-Me,3-Cl	$CH_2CH{=}CH_2$	F	80	95–96	$C_{16}H_{14}ClN_3O$	–	–
I-81	3-C_6H_5O	H	D	25	188–190	$C_{18}H_{13}N_3O_2$	–	–
I-82	2-F[i]	H	D	45	183–184	$C_{13}H_{10}FN_3O$	+	–
I-83	3,4-$(MeO)_2$	$CH_2CH{=}CH_2$	F	55	120–121	$C_{17}H_{17}N_3O_3$	–	–
I-85	3-MeO,4-Me	H	D	15	237–239	$C_{14}H_{13}N_3O_2$	–	–
I-86	3-MeO,4-Me	$CH_2CH{=}CH_2$	F	75	104–105	$C_{17}H_{17}N_3O_2$	–	–
I-88	3,4-$OC(CH_3)_2O$–	H	D	10	223–224	$C_{15}H_{13}N_3O_3$	–	–
I-90	3,4-$C(CH_3){=}C(CH_3)O$–	H	D	30	269–270	$C_{16}H_{13}N_3O_2$	–	–
I-91	3,4-OCH_2O–,6-Me	H	D	30	214–215	$C_{14}H_{11}N_3O_3$	–	–
I-92	3,4-$(CH_2)_3$–	H	D	50	179–180	$C_{15}H_{13}N_3O$	–	–
I-94	3,4-$(CH_2)_3$–	$CH_2CH{=}CH_2$	F	80	81–82	$C_{18}H_{17}N_3O$	–	–
I-95		H	D	10	276–278	$C_{18}H_{17}N_3O_3$	–	–
I-96	3,4-$OC(Et_2)O$–	H	D	15	187–189	$C_{17}H_{17}N_3O_3$	–	–
I-97	3,4-OCH_2O–	$CH_2CH{=}CH_2$,CH_3I	*a*	41	202–203	$C_{17}H_{16}IN_3O_3$	–	–
I-98	3,4-CH_2OCH_2O–	H	D	25	277–279	$C_{14}H_{11}N_3O_3$	–	–
I-99		$CH_2CH{=}CH_2$	F	60	112–113	$C_{21}H_{21}N_3O_3$	–	+
I-100	2,3-$(CH_2)_4$–	H	D	32	265–267	$C_{16}H_{15}N_3O$	–	–
I-101	2,3-$(CH_2)_4$–	$CH_2CH{=}CH_2$	F	80	162–163	$C_{19}H_{19}N_3O$	–	–

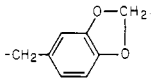
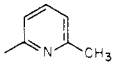
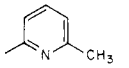
Table IV (*Continued*)

compd	X	R	method	yield, %	mp, °C	formula	analgesic act. sensitive foot	analgesic act. normal foot
I-102	3,4-CH_2OCH_2O-	$CH_2CH{=}CH_2$	F	85	162–163	$C_{17}H_{15}N_3O_3$	–	–
I-103	2,3-OCH_2O-	H	D	60	231–233	$C_{13}H_9N_3O_3$	–	–
I-104	2,3-OCH_2O-	$CH_2CH{=}CH_2$	F	90	143–144	$C_{16}H_{13}N_3O_3$	–	–
I-105	4-COOH	H	D	45	290	$C_{13}H_9N_3O_3$[j]	–	–
I-106	2-F[k]	H	D	70	211–213	$C_{14}H_{10}FN_3O_3$	–	–
I-107	3,4-OCH_2O-[k]	H	D	50	283–285	$C_{15}H_{11}N_3O_5$	–	–
I-108	2-F[l]	H	G	80	316–318	$C_{18}H_8FN_3O{\cdot}CH_3OH$	–	–
I-109	3-COOEt	$CH_2CH{=}CH_2$	F	90	101–102	$C_{18}H_{17}N_3O_3$	–	–
I-110	3-COOEt	H	D	35	193–194	$C_{15}H_{13}N_3O_3$	–	–
I-112	3,4-OCH_2O-[l]	H	*a*	37	325–328	$C_{14}H_9N_3O_5$	–	–
I-113	3,4-OCH_2O-,6-NO_2	H	*a*	68	249–250	$C_{13}H_8N_4O_5$	–	–
I-121	3,4-OCH_2O-	*i*-Pr	F	40	175–176	$C_{16}H_{15}N_3O_3$	++++	++++
I-122	3,4-OCH_2O-	*s*-Bu	F	55	129–131	$C_{17}H_{17}N_3O_3$	–	–
I-123	3,4-OCH_2O-	c-C_5H_9	F	80	156–158	$C_{18}H_{17}N_3O_3$	+++	++
I-124	3,4-OCH_2O-	CF_2CHClF	*a*	18	86–88	$C_{15}H_9ClF_3N_3O_3$	–	–
I-125	3,4-OCH_2O-	$CH(CH_3)CH{=}CH_2$	F	20	106–107	$C_{17}H_{15}N_3O_3$	–	–
I-126	3,4-OCH_2O-	$(CH_2)_2OAc$	*a*	42	111–113	$C_{17}H_{15}N_3O_5$	+	–
I-127	3,4-OCH_2O-	CH_2CH_3	F	72	145–146	$C_{15}H_{13}N_3O_3$	++	–
I-128	3,4-OCH_2O-	CH_2COCH_3	F	40	209–210	$C_{16}H_{13}N_3O_4$	–	–
I-129	3,4-OCH_2O-	CH_2OAc	H	30	141–142	$C_{16}H_{13}N_3O_5$	–	–
I-130	3,4-OCH_2O-	*t*-Bu	*a*	3	142	$C_{17}H_{17}N_3O_3$	++	++
I-132	3,4-OCH_2O-	$CH_2CH(OH)CH_3$	*a*	15	138–139	$C_{16}H_{15}N_3O_4$	++	+
I-134	3,4-OCH_2O-	$CH_2OC_2H_5$	F	90	137–138	$C_{16}H_{15}N_3O_4$	–	–
I-136	H	*n*-Pr	D	70	78–80	$C_{15}H_{15}N_3O$	++	+
I-137	3,4-OCH_2O-	CH_2SCH_3	F	75	149–150	$C_{15}H_{13}N_3O_3S$	+	–
I-138	4-CH_2COOH	H	D	20	295	$C_{14}H_{11}N_3O_3$	–	–
I-139	4-*i*-Bu	H	D	55	193–194	$C_{16}H_{17}N_3O$	–	–
aspirin							+	–
d-propoxyphene							++	+
codeine							+++	++
morphine							++++	++++

[a] Preparation given in the Experimental Section. [b] The results are recorded as follows. In the sensitive or hyperesthetic foot: – = <25 mm at 32 mg/kg; + = 25–34 mm at 32 mg/kg; ++ = >34 mm at 32 mg/kg or 25–34 mm at 16 mg/kg; +++ = >34 mm at 16 mg/kg or 25–34 mm at 8 mg/kg; ++++ = >34 mm at 8 mg/kg. In the normal foot: – = <40 mm at 32 mg/kg; + = 40–49 mm at 32 mg/kg; ++ = >50 mm at 32 mg/kg or 40–49 mm at 16 mg/kg; +++ = 50–59 mm at 16 mg/kg or 40–49 mm at 8 mg/kg; ++++ = >60 mm at 16 mg/kg or >50 mm at 8 mg/kg. [c] Resulted from the 4-acetylamino compound when $COCl_2$ was added. [d] C: calcd, 49.67; found, 50.53. [e] Melting point of ditosyl acid salt. [f] Also 6-amino in pyridine ring. [g] From I-67 by hydrogenation using Pd/C. [h] Also 6-nitro in pyridine ring. [i] Also 6-methyl in pyridine ring. [j] Contains 1.5% water. [k] Also 6-carbomethoxy in pyridine ring. [l] Also 6-carboxy in pyridine ring.

Table V. Miscellaneous Imidazo[4,5-*b*]pyridin-2-ones



compd	R	R′	method	yield, %	mp, °C	formula	analgesic act. sensitive foot	analgesic act. normal foot
I-23	$-(CH_2)_2C_6H_5$	H	D	25	163-164	$C_{14}H_{13}N_3O$	–[a]	–
I-31		H	D	45	236-238	$C_{14}H_{11}N_3O_3$	–	–
I-48	$-CH_2C_6H_4$-4-F	H	D	15	191-192	$C_{13}H_{10}FN_3O$	–	–
I-69		$CH_2CH=CH_2$	F	30	111-112	$C_{15}H_{14}N_4O$	–	–
I-72	c-C_6H_{11}	H	D	25	225-226	$C_{12}H_{15}N_3O$	–	–
I-76		H	D	60	217-219	$C_{12}H_{10}N_4O$	–	–

[a] See footnote *b*, Table IV.

ones showed that there was no correlation of activity with lipophilicity, electronic effect, or steric bulk. The enhancing effect of a 3,4-methylenedioxy substituent appeared to be a specific effect not correlated with any of the above parameters. Compounds I-21, I-121, and I-45, as well as the unsubstituted compound I-15, were the most interesting and were studied more extensively. They were tested in rats in a modification of the Eddy and Leimbach[11b] hot-plate assay. Compounds I-15 and I-21 at 20 mg/kg were several times as potent as *d*-propoxyphene and without showing any overt side effects as shown in Table IX. Despite this analgesic activity the compounds have no propensity to induce physical dependence in mice. This is shown by a lack of withdrawal symptoms after the acute administration of naloxone. Under these experimental conditions compounds such as morphine, codeine, pentazocine, and *d*-propoxyphene all produce physical dependence as revealed by the mice which show excitement and make many "escape jumps". In mice, these naloxone precipitated withdrawal effects provide a valid measure of physical dependence. Absence of these effects indicates a lack of physical dependence capacity. None of the compounds tested induced withdrawal signs. However, they did show significant analgesic activity in mice using the Haffner[11c] tail clamp procedure (see Table X). Naloxone, when given to rats simultaneously with the compound (I-21), did not affect its analgesic activity in the hyperesthesia assay as shown in Table XI.

Two of the compounds (I-15 and I-21) possess activity approaching that of phenylbutazone in both the carrageenan-induced foot edema and adjuvant arthritis assays in the rat.[12a,b] These data are given in Tables XII and XIII. In comparison, *d*-propoxyphene is inactive in the carrageenan edema assay, although it is moderately active in the adjuvant arthritis model.

Experimental Section

All melting points are corrected and were taken on a Thomas-Hoover capillary melting point apparatus. Infrared spectra were obtained from a Nujol mull with a Perkin-Elmer 137 IR spectrometer. A Varian T-60 NMR spepctrometer and an LKB Model 9000 mass spectrometer were also used. All compounds were analyzed for C, H, and N and were within 0.4% of calculated theoretical values unless designated otherwise.

The following chloronitropyridines that could not be purchased were prepared according to the cited literature references: 2,6-dichloro-3-nitropyridine,[13] 2-chloro-3,5-dinitropyridine,[14] 2,5-dichloro-3-nitropyridine,[15] 2-chloro-3-nitro-5-methylpyridine,[16] ethyl 6-chloro-5-nitronicotinate,[17] and 2,4-dichloro-5-nitropyrimidine.[18]

The following anilines that could not be purchased were prepared according to the cited literature references or as designated: 2,3-(methylenedioxy)aniline,[19] 3,4-(ethylenedioxy)aniline,[20] 3,4-(isopropylenedioxy)aniline,[21] 2,3-dimethyl-6-aminobenzofuran,[22] 3,4-(methylenedioxy)-6-methylaniline[23] (aniline prepared from the known nitro compound), 6-amino-1,3-benzodioxan (aniline prepared from the commercial nitro compound), 5-aminophthalan (experimental given), 5-aminospiro[1,3-benzodioxole-2,1′-cyclohexane] and 3,4-[(1,1-diethyl)-methylenedioxy]aniline[21] (anilines prepared from known nitro compounds), and 4-isobutylaniline (experimental given).

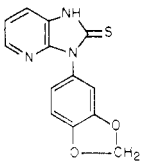
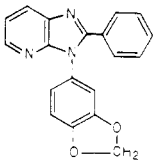
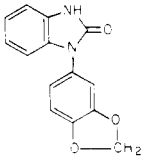
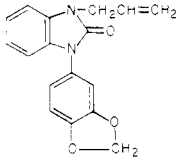
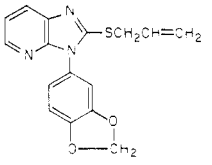
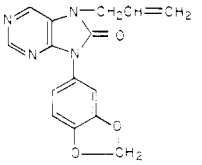
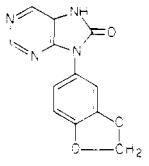
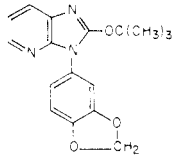
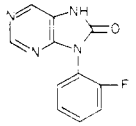
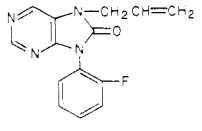
Many of the compounds are prepared by the same general method. These general methods are described by the synthesis of specific compounds. Designation of the method used and the properties of the compounds are given in Tables I–VIII. The preparation of all other new compounds is given specifically for the compounds desired.

Many of the reactions were run only once, and purity rather than yield was the dominating factor.

Reactions of 2-Chloro-3-nitropyridine and Related Compounds with Substituted Anilines. Method A. 2-(3-Chloro-2-methylanilino)-3-nitropyridine (N-43). A mixture of 6.3 g (0.04 mol) of 2-chloro-3-nitropyridine and 16.9 g (0.12 mol) of 3-chloro-2-methylaniline was heated in an oil bath to 170 °C, when the temperature spontaneously rose to 185 °C. After an additional 10 min at 180 °C the mixture was cooled to 50 °C and extracted with a solution of 75 mL of water and 24 mL of HOAc. The insolubles were collected, air-dried, and dissolved in methylene chloride, and the solution was dried, concentrated to a small volume, and diluted with 50 mL of Et_2O which caused crystallization of 6.6 g (63%), mp 134–135 °C.

Method B. 2-[3,4-(Methylenedioxy)anilino]-3-nitropyridine (N-15). A mixture of 6.3 g (0.04 mol) of 2-chloro-3-nitropyridine, 6.8 g (0.05 mol) of 3,4-(methylenedioxy)aniline, and 4.1 g (0.05 mol) of NaOAc in 125 mL of HOAc was stirred and refluxed for 5 h. The reaction mixture was concentrated to about one-fourth of the original volume and diluted with 100 mL of

Table VI. Miscellaneous Structures

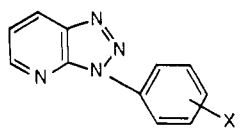
compd	structure	method	yield, %	mp, °C	formula	analgesic act. sensitive foot	analgesic act. normal foot
I-24		*a*	13	285	$C_{13}H_9N_3O_2S$	–[b]	–
I-75		*a*	6	154–155	$C_{19}H_{13}N_3O_2$	–	–
I-84		*a*	24	230–231	$C_{14}H_{10}N_2O_3$	–	–
I-87		F	65	107–109	$C_{17}H_{14}N_2O_3$	–	–
I-89		*a*	58	123–124	$C_{16}H_{13}N_3O_2S$	–	–
I-119		F	65	177–178	$C_{15}H_{12}N_4O_3$	–	–
I-120		*a*	28	274–275	$C_{12}H_8N_4O_3$	–	–
I-131		*a*	61	150–152	$C_{17}H_{17}N_3O_3$	+++	–
I-133		*c*	75	242	$C_{11}H_7FN_4O$	–	–
I-135		F	72	131–132	$C_{14}H_{11}FN_4O$	–	–

[a] Preparation given in the Experimental Section. [b] See footnote *b*, Table IV. [c] Prepared like I-120.

water. The precipitate was collected, 9.5 g (92%), and a small sample was recrystallized from EtOH to give a product melting at 146–148 °C.

2-[3,4-(Methylenedioxy)phenylmethylamino]-3-nitropyridine (N-31). To 18 g (0.12 mol) of piperonylamine was added portionwise 6.3 g (0.04 mol) of 2-chloro-3-nitropyridine. The reaction is exothermic and so it was cooled occasionally. After all had been added, the reactants had solidified. It was heated

Table VII. 3-(Substituted phenyl)triazolopyridines[a]



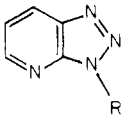
compd	X	yield, %	mp, °C	formula	analgesic act. sensitive foot	analgesic act. normal foot
T-1	2-F	60	118-119	$C_{11}H_7FN_4$	+++[b]	–
T-2	H	25	76-77	$C_{11}H_8N_4$	–	–
T-3	4-MeO	35	129-130	$C_{12}H_{10}N_4O$	–	–
T-4	4-F	50	182-184	$C_{11}H_7FN_4$	–	–
T-5	2-*i*-Pr	20	oil	$C_{14}H_{14}N_4$	+	–
T-6	2,6-Me_2	60	155-156	$C_{13}H_{12}N_4$[c]	+	–
T-7	3-CF_3	30	100	$C_{12}H_7F_3N_4$	+	–
T-8	2,4-F_2	30	138-139	$C_{11}H_6F_2N_4$	+++	++
T-9	2-Cl	25	100-101	$C_{11}H_7ClN_4$	+	–
T-10	2-Me_2N	40	78-79	$C_{13}H_{13}N_5$	–	–
T-11	3-F	40	144-145	$C_{11}H_7FN_4$	–	–
T-13	2-F,5-Me	25	107-108	$C_{12}H_9FN_4$	–	–
T-14	4-Me	20	114-115	$C_{12}H_{10}N_4$	–	–
T-15	3,4-OCH_2O-	16	169-170	$C_{12}H_8N_4O_2$	+	+
T-16	4-NHAc	15	187-188	$C_{13}H_{11}N_5O$	–	–
T-17	2,4-Me_2	35	124-125	$C_{13}H_{12}N$	–	–
T-18	2,5-F_2	70	144-145	$C_{12}H_6F_2N_4$	++	–
T-22	2-Br	70	116-118	$C_{11}H_7BrN_4$	+	–
T-25	3,4-$O(CH_2)_2O$-	65	162-164	$C_{13}H_{10}N_4O_2$	++	–
T-26	2,4-Cl_2	35	150-151	$C_{11}H_6Cl_2N_4$	–	+
T-27	2,6-F_2	15	173-174	$C_{11}H_6F_2N_4$	+	–
T-28	4-Cl	35	162-163	$C_{11}H_7ClN_4$	–	–
T-30	3,4-$(MeO)_2$	60	137-138	$C_{13}H_{12}N_4O_2$	–	–
T-43	2-Me,3-Cl	20	152-153	$C_{12}H_9ClN_4$	–	–
T-47	3,4-Cl_2	60	175-176	$C_{11}H_6Cl_2N_4$	–	–
T-49	3,4,5-$(MeO)_3$	20	138-140	$C_{14}H_{14}N_4O_3$	–	–
T-50	2,4-$(MeO)_2$	45	163-164	$C_{13}H_{12}N_4O_2$	–	–
T-59	4-C_6H_5O	50	60-61	$C_{17}H_{12}N_4O_2$	–	–
T-65	3,4-CH_2OCH_2-	15	174-175	$C_{13}H_{10}N_4O$	–	–
T-68	3-MeO	45	78-80	$C_{12}H_{10}N_4O$	–	–
T-74	2,5-$(MeO)_2$	70	140-142	$C_{13}H_{12}N_4O_2$	–	–
T-77	3,4-Me_2	70	110-111	$C_{13}H_{12}N_4$	–	–
T-82	2-F[d]	75	122-123	$C_{12}H_9FN_4$	–	–
T-85	3-MeO,4-Me	25	132-133	$C_{13}H_{12}N_4O$	–	–
T-88	3,4-$OC(CH_3)_2O$-	10	122-123	$C_{14}H_{12}N_4O_2$	–	–
T-90	3,4-$C(CH_3)=C(CH_3)O$-	10	152-153	$C_{15}H_{12}N_4O$	–	–
T-91	3,4-OCH_2O-,6-Me	80	147-148	$C_{13}H_{10}N_4O_2$	–	–
T-92	3,4-$(CH_2)_3$-	35	133-134	$C_{14}H_{12}N_4$	–	–
T-96	3,4-$OC(Et_2)O$-	65	56-57	$C_{16}H_{16}N_4O_2$	–	–
T-98	3,4-CH_2OCH_2O-	60	183-184	$C_{13}H_{10}N_4O_2$	–	–
T-105	4-COOH	35	292	$C_{12}H_8N_4O_2$[e]	–	–
T-106	2-F[f]	40	112-113	$C_{13}H_9FN_4O_2$	–	–
T-107	3,4-OCH_2O-[f]	15	189-191	$C_{14}H_{10}N_4O_4$	–	–
T-110	3-COOEt	70	114-115	$C_{14}H_{12}N_4O_2$	–	–
T-139	4-*i*-Bu	65	40-42	$C_{15}H_{16}N_4$	–	–
T-140	2-MeO	60	154-155	$C_{12}H_{10}N_4O$	+	–
T-142	H[g]	15		*h*	–	–
T-143	2-F[i]	65	132-133	$C_{11}H_6ClFN_4$	+	–
T-144	3-CN	20	165-166	$C_{12}H_7N_5$	–	–
T-145	4-Me_2N	15	139-141	$C_{13}H_{13}N_5$[j,k]	–	–
T-146	3-$CONH_2$	75	237-239	$C_{12}H_9N_5O$	+	–
T-147	4-$COCH_3$	80	184-185	$C_{13}H_{10}N_4O$	–	–
T-148	2-OH	44	165-166	$C_{11}H_8N_4O$[l]	–	–
T-149	4-Et	65	61-62	$C_{13}H_{12}N_4$	–	–
T-150	2-CN	75	177-179	$C_{12}H_7N_5$[l]	+	–
T-151	2-C(=O)NH_2	45	>340	$C_{12}H_9N_5O$[l]	+	–

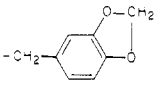
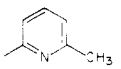
[a] All the examples were prepared by method I unless designated otherwise. [b] See footnote *b*, Table IV. [c] C: calcd, 70.08; found, 69.63. [d] Also 6-methyl in pyridine ring. [e] Contains 1% water. [f] Also 6-carbomethoxy in pyridine ring. [g] Also 5-chloro in pyridine ring. [h] Reference 5. [i] Also 6-chloro in pyridine ring. [j] N: calcd, 29.27; found, 28.62. [k] Prepared by method K. [l] Preparation given in the Experimental Section.

on the steam bath 15 min. EtOH (25 mL) was then added and heating continued for 20 min. Water was slowly added to give a complete solution. Upon cooling a yellow solid crystallized: 10.1 g (32%); mp 113–115 °C.

2-(2-Fluorobenzylamino)-3-nitropyridine (N-48). To a solution of 6.3 g (0.04 mol) of 2-chloro-3-nitropyridine in 100 mL of benzene was added 10.4 g (0.082 mol) of 2-fluorobenzylamine. The solution began to get cloudy after a few minutes. It was heated on the steam bath and a solid began to crystallize. After 1 h the HCl salt of the starting benzylamine was removed by filtration (4.1 g). The filtrate was heated for another hour and another 1.3 g of hydrochloride was removed. After another hour

Table VIII. 3-Substituted Triazolopyridines[a]



compd	R	yield, %	mp, °C	formula	analgesic act. sensitive foot	analgesic act. normal foot
T-31		55	107-108	$C_{13}H_{10}N_4O_2$	–[b]	–
T-48	$-CH_2C_6H_4$-2-F	20	84-85	$C_{12}H_9FN_4$	–	–
T-76		70	141-142	$C_{11}H_9N_5$	–	–
T-141		45	195-197	$C_{10}H_7N_5$	–	–
T-152	$-(CH_2)_2C_6H_5$	35	69-70	$C_{13}H_{12}N_4$	–	–

[a] All compounds were prepared by method I. [b] See footnote *b*, Table IV.

Table IX. Analgesic Activity in the Rat Hot-Plate Assay[a]

compd	dose, mg/kg, oral aq suspn	increase in mean reaction time (s) over control times 1 h	2 h	3 h	4 h	5 h
I-21	5	0.1	3.8	5.3	3.9	0
	10	8.8	7.3	11.6	7.1	6.2
	20	13.5	21.7	24.4	28.1	24.5
d-propoxyphene	30	−3.2	−2.6	−2.2	−0.8	2.4
	60	−3	−0.8	−2.4	−0.8	−1.0
	120	41.9	30	24.5	15	3.6
control times		7.7	6.6	6.6	5.7	6.2
I-15	5	1.5	2.1	−0.1	1.3	0.4
	10	2.0	3.9	2.8	2.3	−0.2
	20	6	15	20.4	20	18.3
d-propoxyphene	30	6.5	0.7	−4.4	0.2	0.1
	60	8.7	4.4	0.2	1.8	−1.1
	90	40.6[b]	42[b]	40.7[b]	36.4[b]	10.5[b]
control times		7.9	9.3	16.3	13.6	13.5

[a] The assay is described in ref 11b. The temperature of the hot plate was maintained at 58 °C. Instead of mice, young Sprague-Dawley rats (ten per dose level) were used. [b] Sedation was evident at all time intervals; six of ten animals succumbed prior to 5-h reading.

of heating the cloudy mixture was filtered through Super cel and concentrated to about 30 mL. Upon the addition of 50 mL of petroleum ether the product crystallized: yield 8.1 g (83%); mp 116–118 °C.

3,5-Dinitro-2-(2-fluoroanilino)pyridine (N-67). When 2.0 g (0.01 mol) of 2-chloro-3,5-dinitropyridine and 3 mL (0.03 mol) of 2-fluoroaniline were mixed the temperature of the mixture rose to 80 °C. The reaction was completed by heating the mixture on the steam bath for 15 min, and then the solid product was crystallized from MeOH to give 850 mg (31%), mp 159–161 °C.

1-[3,4-(Methylenedioxy)anilino]-2-nitrobenzene (N-84). A mixture of 12.6 g (0.08 mol) of 2-chloronitrobenzene and 21.9 g (0.17 mol) of 3,4-(methylenedioxy)aniline was stirred and heated in an oil bath to 220 °C when there was an exotherm to 245 °C. The dark reaction mixture was cooled and extracted with ether. The ether extract was washed once with 50 mL of 1 N HCl, dried, and finally evaporated to a small volume. Petroleum ether was added to precipitate a deep red solid which was crystallized from ethanol. There was obtained 3.5 g (17%) of deep red rods, mp 109–111 °C.

Methyl 6-(2-Fluoroanilino)-5-nitronicotinate (N-106). A mixture of 1 g (0.0046 mol) of methyl 6-chloro-5-nitronicotinate and 2 mL of 2-fluoroaniline was heated on the steam bath for 90 min. MeOH (15 mL) was added and the solid removed by filtration. Crystallization from MeOH gave 600 mg (45%), mp 145–148 °C.

2-Chloro-4-[3,4-(methylenedioxy)anilino]-5-nitropyrimidine (N-120). To 15 g (0.078 mol) of 2,4-dichloro-6-nitropyrimidine in 100 mL of ether was added over 1 h a solution of 22 g (0.16 mol) of 3,4-(methylenedioxy)aniline in 100 mL of ether. A deep red solid formed during the addition and finally the mixture was so thick that more ether was added to facilitate stirring. After a further 2 h of stirring at room temperature the solid was removed and washed well with warm water. It was dissolved in 150 mL of hot $CHCl_3$ and clarified by filtration. After concentration to about 75 mL, ether was added to promote crystallization: yield 16.5 g (73%); mp 143–145 °C.

Hydrogenation Reactions. Method C. 3-Amino-2-[3,4-(methylenedioxy)anilino]pyridine. The crude nitro compound N-15 (9.5 g) was hydrogenated at 3 atm in 175 mL of MeOH using 0.5 g of 5% Pd/C as a catalyst, the theoretical amount of hydrogen being consumed in 16 h. The catalyst was removed, the filtrate was concentrated in vacuo, and the dark residue was extracted with 75 mL of 2.5 N HCl and 75 mL of H_2O. The crude acid solution was used in methods D and I.

1,3-Dihydro-3-[3,4-(methylenedioxy)phenyl]-1-propylimidazo[4,5-*b*]pyridin-2-one (I-45). I-21 (1 g) was hydrogenated at 3 atm in 30 mL of EtOH over 100 mg of PtO_2 as catalyst for 1.5 h. The catalyst was removed and the filtrate concentrated to a small volume. The product crystallized and was collected to give 800 mg (80%), mg 112–114 °C.

5-Aminophthalan. The 5-nitrophthalan (19 g) was hydrogenated at 3 atm in 200 mL of MeOH over 1 g of 5% Pd/C for 30 min. The catalyst was removed by filtration and the filtrate

Table X. Lack of Physical Dependence as Shown by Abrupt Withdrawal with Naloxone[a]

compd	dose, mg/kg po, aq suspn	no. of mice with analgesia	no. of mice with escape jumps	total no. of jumps
I-15	75	8/10	0/10	0
	50	6/10	0/10	0
	25	5/10	2/10	21
	12.5	4/10	1/10	1
d-propoxyphene	75	7/10	8/10	159
	50	7/10	7/10	78
	25	7/10	7/10	86
	12.5	5/10	7/10	63
methocel (control)		0/10	2/10	3
I-21	75	5/10	0/10	0
	50	5/10	1/10	1
	25	5/10	1/10	21
	12.5	2/10	2/10	12
d-propoxyphene	75	7/10	9/10	78
	50	5/10	8/10	98
	25	3/10	3/10	15
	12.5	2/10	2/10	14
methocel (control)		0/10	2/10	10

[a] The mice are given the test compound and tested 2 h later for analgesia (Haffner clamp). Three hours after administration of the test compound the mice are abruptly withdrawn with naloxone, 10 mg/kg ip.

Table XI. Lack of Physical Dependence as Shown by Simultaneous Treatment with Naloxone[a]

pretreatment	treatment	dose, mg/kg po, aq suspn	mean pain reaction threshold in mmHg ($N = 8$) inflamed foot	mean pain reaction threshold in mmHg ($N = 8$) normal foot
methocel	– (control)		18.3	35.3
methocel	I-21	5	28.8	40.5
methocel	I-21	10	44.4	52.3
methocel	I-21	20	74.4	88.5
naloxone	– (control)		19.4	34.5
naloxone	I-21	5	33.4	38.4
naloxone	I-21	10	47.8	71.1
naloxone	I-21	20	66.6	79.3

[a] The standard hyperesthesia test protocol was used. Two groups of six Sprague-Dawley rats were randomly administered various dose levels of I-21 1 h before testing. Fifteen minutes prior to testing, one group was administered naloxone (5.0 mg/kg ip); the other group was given methocel.

Table XII. Rat Foot Carrageenan Edema Activity[a]

compd	dose, mg/kg, oral suspn	% inhibn of edema
I-15	30	54, 38, 37
I-21	30	49, 57, 42
phenylbutazone	30	58, 49, 41, 39, 49
d-propoxyphene	30	23, 32

[a] The standard assay, ref 12a, was used with Sprague-Dawley rats, six rats per test.

was evaporated to dryness to give 15.1 g (97%), mp 102–104 °C. Recrystallization from C_6H_6–petroleum ether raised the melting point to 104–105 °C. Anal. (C_8H_9NO) C, H, N.

5-Amino-4-[3,4-(methylenedioxy)anilino]pyrimidine. A solution of 7.2 g (0.025 mol) of N-120 in 250 mL of EtOH was hydrogenated at 3 atm in the presence of 1.5 g of 5% Pd/C and 2.94 g (0.03 mol) of KOAc. Only one-third of the calculated hydrogen pressure drop was recorded in 3.5 h, so another 1.5 g of Pd/C was added and the mixture heated to 75 °C. In another 3 h another one-third of the theoretical hydrogen pressure drop was recorded and so a third sample of 1.5 g of Pd/C was added and the mixture again heated to 75 °C for 7 h. The theoretical hydrogen pressure drop was attained. The catalyst was removed and 50 mL of 2.5 N HCl was added to the filtrate. This was concentrated to a small volume and a brown solid separated which was collected. This was suspended in 50 mL of water, an excess of $NaHCO_3$ was added, and the mixture was stirred for 30 min. The brown solid was collected which weighed 1.7 g (33%) and melted at about 183 °C. The IR showed NH_2 bands and the Beilstein test for chlorine was negative. This was used in the next step.

Table XIII. Adjuvant Arthritis Activity[a]

compd	dose, mg/kg po, agar suspn	% inhibn of swelling
I-15	50	68.3
I-21	50	78.2
phenylbutazone	50	78
d-propoxyphene	50	56.2

[a] On day 0 female Lewis rats (ten per group) weighing 170–190 g are sensitized in the right hind foot pad subplantar with 0.1 mL of a suspension containing mycobacterium butyricum in light mineral oil. Compounds are viritized in 0.25% sterile agar and administered orally on days 1–13. Foot volume of the paws is measured on day 0 and 14. Percent inhibition of swelling is determined.

4-Isobutylaniline. 4-Nitroisobutylbenzene (20 g) was hydrogenated at 3 atm in 250 mL of EtOH in the presence of 0.5 g of 5% Pd/C for 16 h. The catalyst was removed by filtration and the filtrate concentrated to a dark oil (15.5 g, 87%) which was completely soluble in 2.5 N HCl. This crude material was used in the reaction with 2-chloro-3-nitropyridine.

2,2-Diethyl-5-amino-1,3-benzodioxole. A solution of 14.1 g of 2,2-diethyl-5-nitro-1,3-benzodioxole in 200 mL of MeOH was hydrogenated at 3 atm in the presence of 0.5 g of 5% Pd/C for 1.5 h. The product was isolated and used in the reaction with 2-chloro-3-nitropyridine.

5-Aminospiro[1,3-benzodioxole-2,1′-cyclohexane]. A solution of 20 g of 5-nitrospiro[1,3-benzodioxole-2,1′-cyclohexane] in 250 mL of MeOH was hydrogenated at 3 atm in the presence of 1 g of 5% Pd/C. After 3 h the hydrogen uptake was completed, and the amine was then isolated and used dirrectly in the next reaction.

2-[3,4-(Methylenedioxy)anilino]aniline. N-84 (11 g) was hydrogenated at 3 atm in 175 mL of MeOH using 0.5 g of 5% Pd/C. After 16 h the theoretical amount of hydrogen was absorbed, the catalyst was removed, and 75 mL of 2.5 N HCl was quickly added to the filtrate. Most of the MeOH was taken off in vacuo and the solution containing the *o*-diamine was used for the reaction with phosgene.

Formation of Imidazo[4,5-*b*]pyridin-2-ones and Related Compounds. Method D. 1,3-Dihydro-3-[3,4-(methylenedioxy)phenyl]imidazo[4,5-*b*]pyridin-2-one (I-15). About one-third of the acid solution from method C (i.e., ~3 g of the product) was treated with phosgene gas for 30 min and the dark solution was allowed to stand at room temperature overnight. NH_4OH was added dropwise with stirring to the ice-cold reaction mixture until alkaline. The precipitate was collected and extracted with 50 mL of 2.5 N NaOH. The alkaline solution was treated with decolorizing charcoal and the filtrate therefrom was acidified with HOAc. The precipitate (1.1 g) was collected and recrystallized from DMF–Et_2O to give 900 mg (30%), mp 259–260 °C.

Method E. 1,3-Dihydro-3-(2-fluorophenyl)imidazo[4,5-*b*]pyridin-2-one (I-1). A mixture of 2.7 g of 3-amino-2-(2-fluoroanilino)pyridine hydrochloride and 3 g of urea was heated at 180 °C for 25 min. After cooling, the residue was stirred with 50 mL of 2.5 N NaOH. The alkaline solution was treated with charcoal and filtered. The filtrate was made acidic with HOAc which caused crystallization of the product (1 g, mp 195 °C). This was recrystallized from EtOAc–petroleum ether to give 800 mg (31%), mp 199–202 °C.

1,3-Dihydro-[3,4-(methylenedioxy)phenyl]imidazo[4,5-*b*]pyridine-2-thione (I-24). A mixture of 2.6 g (0.01 mol) of

3-amino-2-[3,4-(methyldioxy)anilino]pyridine hydrochloride, 1.8 g (0.011 mol) of potassium ethyl xanthate, and 840 mg (0.01 mol) of $NaHCO_3$ in 45 mL of EtOH and 10 mL of H_2O was heated at reflux for 3.5 h. There was added 3 mL of 2.5 N NaOH and the mixture was filtered. The filtrate was acidified with HOAc and the precipitated product was collected: 500 mg (13%); mp 278 °C. After recrystallization from dioxane the product melted at 285 °C.

1-[3,4-(Methylenedioxy)phenyl]-2-benzimidazolinone (I-84). The aqueous acid solution containing crude 2-[3,4-(methylenedioxy)anilino]aniline was reacted with an excess of phosgene for 30 min. The reaction was cooled and treated with an excess of NH_4OH. A gum formed which was crystallized twice from dioxane–petroleum ether to give 700 mg (24%) of product melting at 230–231 °C.

1,3-Dihydro-3-[3,4-(methylenedioxy)phenyl]imidazo-[4,5-*d*]pyrimidin-2-one (I-120). The above crude *o*-diamine (1.7 g) from the hydrogenation of N-120 was mixed with 10 g of urea and heated in an oil bath under a blanket of N_2. The internal temperature was maintained at 190 °C for 15 min. After cooling to 90 °C, 50 mL of water was added and the solid collected. This crude solid was extracted with 25 mL of 2.5 N NaOH. The filtered extract was treated with Darco and HOAc added to precipitate the product, which weighed 1.1 g. It was crystallized from 125 mL of boiling dioxane to give 500 mg (28%), mp 274–275 °C. The mass spectrum gives a molecular ion of 256.

Alkylations. Method F. 1,3-Dihydro-1-allyl-3-[3,4-(methylenedioxy)phenyl]imidazo[4,5-*b*]pyridin-2-one (I-21). To a suspension of 500 mg (0.002 mol) of I-15 in 50 mL of Me_2CO was added 220 mg (0.004 mol) of powdered KOH. After being stirred for 15 min 480 mg (0.004 mol) of allyl bromide was added. After 1 h of stirring at room temperature, the mixture was heated on a steam bath to evaporate about half the solution. Water was added to precipitate a solid (500 mg, mp ~100 °C). After recrystallization from C_6H_6–petroleum ether there was obtained 400 mg (69%), mp 130–131 °C.

1,3-Dihydro-1-(ethoxycarbonylmethyl)-3-[3,4-(methylenedioxy)phenyl]imidazo[4,5-*b*]pyridin-2-one (I-38) and 1,3-Dihydro-1-(carboxymethyl)-3-[3,4-(methylenedioxy)-phenyl]imidazo[4,5-*b*]pyridin-2-one (I-51). To a stirred suspension of 2 g (0.008 mol) of I-15 in 100 mL of Me_2CO was added 980 mg (0.016 mol) of powdered KOH. After being stirred at room temperature for 30 min 1.7 g (0.01 mol) of ethyl bromoacetate was added over 3 min. After 3 h at room temperature and 5 min on the steam bath, the Me_2CO was evaporated. The residue was extracted with H_2O leaving 700 mg of solid. Crystallization from C_6H_6–petroleum ether gave 500 mg (18%) of I-38, mp 144–146 °C.

The H_2O extract from above was acidified with HOAc. The precipitated solid (1 g) was extracted with a solution of 50 mL of H_2O and 20 mL of NH_4OH. The extract was acidified with HOAc. The precipitate was recrystallized from 60 mL of EtOH to give 450 mg (18%) of I-51, mp 283 °C.

1-Allenyl-1,3-dihydro-3-[3,4-(methylenedioxy)phenyl]-imidazo[4,5-*b*]pyridin-2-one (I-40) and 1-(2-Chloroallyl)-1,3-dihydro-3-[3,4-(methylenedioxy)phenyl]imidazo[4,5-*b*]pyridin-2-one (I-39). A mixture of 1.0 g (0.0039 mol) of I-15, 100 mL of Me_2CO, and 220 mg (0.039 mol) of powdered KOH was stirred at room temperature 5 min and to it was added 960 mg (0.0085 mol) of 2,3-dichloropropene. The mixture was refluxed for 20 h. H_2O (100 mL) was added and after standing overnight it was filtered and the product crystallized from 35 mL of EtOAc. There was obtained 170 mg (15%) of I-40, mp 195–196 °C. The Me_2CO–H_2O filtrate was concentrated to remove the Me_2CO. The remaining solution was extracted with 4 × 20 mL of CH_2Cl_2. The combined extracts were dried and concentrated to an oil. Trituration with hexane caused crystallization. Crystallization from EtOAc–hexane and from MeOH gave 100 mg (7.8%) of I-39, mp 122–123 °C.

1,3-Dihydro-3-[3,4-(methylenedioxy)phenyl]-1-(2-thiazolinyl)imidazo[4,5-*b*]pyridin-2-one (I-54). A suspension of 1.2 g (0.0047 mol) of I-15 in 100 mL of dry dimethoxyethane was stirred and treated with 336 mg (0.007 mol) of a 50% NaH emulsion. After 15 min at room temperature, there was added 850 mg (0.007 mol) of 2-chloroethyl isothiocyanate and the mixture was refluxed 3 h. Most of the solvent was evaporated and the residue was diluted with 40 mL of 1 N NaOH. The precipitate was recrystallized from 5 mL of dioxane–Et_2O to give 450 mg (30%), mp 224–226 °C.

1,3-Dihydro-1-hydroxymethyl-3-[3,4-(methylenedioxy)-phenyl]imidazo[4,5-*b*]pyridin-2-one (I-58). A mixture of 500 mg of I-15 and 30 mL of 37% formaldehyde was heated on the steam bath for 1.5 h. The hot solution was treated with decolorizing carbon and filtered, and the filtrate was treated with 2 mL of 2.5 N NaOH and 30 mL of H_2O. The precipitate weighed 400 mg (72%), mp 268 °C.

2-Allylthio-3-[3,4-(methylenedioxy)phenyl]imidazo[4,5-*b*]pyridine (I-89). A solution of 1.8 g of I-24 in 50 mL of 2.5 N NaOH and 30 mL of water was stirred vigorously as 1 mL of allyl bromide was added. A light tan solid formed after a short time and stirring was continued for 30 min. The crude product was collected and crystallized from C_6H_6–petroleum ether giving 1.2 g (58%) of white needles melting at 123–124 °C. The NMR is in accord with *S*-allyl rather than *N*-allyl: NMR ($CDCl_3$) δ 4.02 (d, 2-SCH_2) whereas for -NCH_2- δ would be ~4.55.

1-(2-Chloro-1,1,2-trifluoroethyl)-1,3-dihydro-3-[3,4-(methylenedioxy)phenyl]imidazo[4,5-*b*]pyridin-2-one (I-124). A mixture of 1.3 g (0.005 mol) of I-15, 3 g of 1-chloro-1,2,2-trifluoroethylene, and 50 mg (0.009 mol) of NaOMe as catalyst in 40 mL of DMF was heated in a bomb at 80 °C for 5 h. The yellow solution was concentrated to a small volume and a mixture of 5 mL of 2.5 N NaOH and 75 mL of H_2O was added. The solid was collected and recrystallized twice from C_6H_6–petroleum ether: 350 mg (18%); mp 86–88 °C.

1,3-Dihydro-1-*tert*-butyl-3-[3,4-(methylenedioxy)-phenyl]imidazo[4,5-*b*]pyridin-2-one (I-130) and 2-*tert*-Butoxy-3-[3,4-(methylenedioxy)phenyl]imidazo[4,5-*b*]-pyridine (I-131). To a stirred suspension of 2.5 g (0.01 mol) of I-15 in 150 mL of acetone was added 1.12 g (0.02 mol) of powdered KOH. This was stirred at room temperature for 10 min and 2.74 g (0.02 mol) of *tert*-butyl bromide was added. After refluxing for 36 h and then evaporation, the residue was extracted with 25 mL of 2.5 N NaOH and 100 mL of H_2O. There was a small amount of insoluble oil which solidified. This weighed 150 mg and was a mixture of the *N-tert*-butyl and *O-tert*-butyl derivatives. The solid was placed on a silica gel GF prep plate (1000 μ) and eluted with a solution of hexane–ether (2:1). The *O-tert*-butyl isomer moved the faster. The isomers were easily distinguished by their IR spectra. The *N-tert*-butyl isomer I-130, 90 mg (3%), melted at 142 °C and then solidified and melted again at 258–259 °C. The mass spectrum gave a molecular ion of 311. Anal. C: calcd, 65.58; found, 64.71. The *O-tert*-butyl isomer I-131, 35 mg (1.1%), melted at 150–152 °C.

Nitration Reactions. 5-Nitrophthalan. Phthalan (6 g, 0.05 mol) was dissolved in 75 mL of concentrated H_2SO_4 and cooled to 5 °C, and with stirring a solution of 5.1 g (0.05 mol) of KNO_3 in 25 mL of concentrated H_2SO_4 was added dropwise over 40 min while maintaining the temperature at <7 °C. After an additional 30 min at ice-bath temperature and 30 min at room temperature, the solution was poured onto ice. The precipitate was collected and recrystallized from C_6H_6–petroleum ether to give 5.5 g (67%): mp 90–92 °C; NMR δ 8.15 (m, 1, J = 2 Hz, aromatic proton 6), 8.1 (s, 1, aromatic proton 4), 7.40 (d, 1, J = 8 Hz, aromatic proton 7), 5.17 (s, 4, -CH_2OCH_2-). Anal. ($C_8H_7NO_3$) C, H, N.

5-Nitrospiro[1,3-benzodioxole-2,1′-cyclohexane]. While 200 mL of 70% HNO_3 was stirred and cooled to 0 °C, 19.5 g of spiro[1,3-benzodioxole-2,1′-cyclohexane][19] was added over 1 h. The nitro compound formed as a precipitate during the acid addition. This was stirred another 15 min at 0 °C and poured into ice water. The yellow nitro compound was collected and recrystallized from hexane giving 17.9 g (74%): mp 99–100 °C; NMR ($CDCl_3$) δ 7.83 (m, 1, aromatic proton 6), 7.55 (d, 1, J = 2 Hz, aromatic proton 4), 6.75 (d, 1, J = 8.9 Hz, aromatic proton 7), 1.75 [m, 10, -$(CH_2)_5$-].

2,2-Diethyl-5-nitro-1,3-benzodioxole. 2,2-Diethyl-1,3-benzodioxole[19] (14 g) was added with good stirring to 140 mL of 70% HNO_3 at 0 °C over 30 min. The reaction mixture was stirred another 20 min at 0 °C and then poured onto ice. The oil that separated was extracted with Et_2O which was washed with aqueous $NaHCO_3$. The Et_2O was evaporated and the oil was taken up in petroleum ether and cooled in dry ice to crystallize the product: 14.5 g (82%); mp 30–31 °C. Anal. ($C_{11}H_{13}NO_4$) C, H, N.

1,3-Dihydro-3-[3,4-(methylenedioxy)-6-nitrophenyl]-imidazo[4,5-*b*]pyridin-2-one (I-113). To 7 mL of HNO_3 (d = 1.5) with stirring and ice cooling was added portions of 500 mg of I-15 over 10 min. The solution was kept another 5 min at ice temperature and then poured onto ice. A yellow solution formed which soon crystallized. The product was collected and washed with $NaHCO_3$ solution. This was recrystallized from DMF–Et_2O giving 400 mg (68%) of yellow crystals: mp 249–250 °C; NMR (DMF-d_7) δ 7.94 (dd, 1, J = 1.5 Hz, α-H on pyridine), 7.78 (s, 1, α to NO_2), 7.48 (dd, 1, γ-H on pyridine), 7.39 (s, 1, β to NO_2), 7.10 (dd, 1, J = 5.0 Hz for α–β, J = 7.6 Hz for β–γ, β proton on pyridine).

4-Nitroisobutylbenzene. To 200 g (1.5 mol) of rapidly stirred isobutylbenzene was added dropwise a solution of 95 mL of 70% HNO_3 and 95 mL of concentrated H_2SO_4. Two layers were always present. The temperature was kept below 32 °C using occasional cooling. The addition took 5.5 h. The mixture was then stirred overnight. To the two layers were then added 200 mL of ice and 100 mL of hexane. The organic layer was separated and washed with water and with a $NaHCO_3$ solution until all the acid was neutralized. It was then dried, the hexane evaporated, and the yellow liquid distilled twice at 1 mm; the fraction, 69.5 g (26%), boiling at 105–107 °C was shown to be the correct isomer by a study of its NMR spectra [NMR ($CDCl_3$) δ 8.12 (d, 2, J = 8.8 Hz), 7.31 (d, 2, J = 8.8 Hz)]. This was used in the next experiment.

Miscellaneous Reactions. Method G. 1,3-Dihydro-3-[3,4-(methylenedioxy)phenyl]-2-oxoimidazo[4,5-*b*]pyridine-6-carboxylic Acid (I-112). Compound I-107 (500 mg) was warmed on the steam bath for 3 h with 5 mL of 2.5 N NaOH. The cooled solution was neutralized with 5 mL of 2.5 N HCl. A gelatinous precipitate was removed by filtration and dried. Repeated extraction with boiling MeOH and then concentration of the combined MeOH extract gave 200 mg (37%) of product, mp 325–328 °C. This contained 1 mol of MeOH which was lost by a thermal gravimetric analysis at 140 °C. Anal. C: calcd, 54.38; found, 53.81.

Method H. 1,3-Dihydro-1-(β-acetoxyethyl)-3-[3,4-(methylenedioxy)phenyl]imidazo[4,5-*b*]pyridin-2-one (I-126). A mixture of I-60 (250 mg) and Ac_2O (10 mL) was heated under reflux for 2 h. The solvents were removed in vacuo and the resulting oil was dissolved in Et_2O and washed with $NaHCO_3$ solution. The Et_2O solution was dried and evaporated. The gum was crystallized from CH_2Cl_2 by the addition of hexane: 120 mg (42%); mp 111–113 °C.

Method I. 3-[3,4-(Methylenedioxy)phenyl]-3*H*-1,2,3-triazolo[4,5-*b*]pyridine (T-15). About two-thirds of the solution described in method C was diluted with 25 mL of EtOH. This was stirred and cooled to 0 °C. Some of the hydrochloride precipitated, but a solution of 1.3 g of $NaNO_2$ in 30 mL of water was slowly added. The product began to precipitate and after 20 min at room temperature 3 g of crude brown solid was removed by filtration. This was dissolved in 150 mL of warm C_6H_6 and treated with charcoal and then with 10 g of Al_2O_3. The filtrate was concentrated to a small volume and 900 mg (16%) of product crystallized by the addition of petroleum ether, mp 169–170 °C.

Method J. 3-(2-Cyanophenyl)-1,2,3-triazolo[4,5-*b*]pyridine (T-150). A mixture of 1 g (0.0036 mol) of T-22 and 1 g (0.01 mol) of CuCN in 10 mL of dry N-methylpyrrolidinone was purged with nitrogen and heated in an oil bath at 175 °C for 3 h. After cooling to 50 °C a mixture of 40 mL of NH_4OH and 40 mL of water was added. The precipitate was collected and washed with NH_4OH–H_2O (1:1) and H_2O and air-dried. The solid was extracted with 40 mL of hot C_6H_6. The C_6H_6 extract was cooled and diluted slightly with petroleum ether to give 600 mg (75%), mp 177–179 °C.

Method K. 3-(2-Carbamoylphenyl)-1,2,3-triazolo[4,5-*b*]pyridine (T-151). T-150 (600 mg) was dissolved in 8 mL of concentrated H_2SO_4 with ice cooling. After standing at room temperature for 7 h it was poured onto ice. The cold solution was treated with an excess of NH_4OH. The precipitate was collected, air-dried, and recrystallized from DMF–H_2O to give 300 mg (45%), mp >340 °C.

1,3-Dihydro-1-(morpholinocarbonylmethyl)-3-[3,4-(methylenedioxy)phenyl]imidazo[4,5-*b*]pyridin-2-one (I-61). A mixture of 600 mg (0.0019 mol) of I-51 and 10 mol of thionyl chloride was heated on a steam bath for 3 h. The mixture was evaporated to dryness, the residue was dissolved in Et_2O, and a slight excess of morpholine was added. The mixture was diluted with H_2O and the precipitate was recrystallized from 10 mL of MeOH to give 100 mg (14%), mp 212–213 °C.

1,3-Dihydro-3-[3,4-(methylenedioxy)phenyl]-2-oxoimidazo[4,5-*b*]pyridine-1-*n*-butylcarboxamide (I-71). A suspension of 1.2 g (0.0047 mol) of I-15 in 75 mL of dry dimethoxyethane was treated with 1 g (0.01 mol) of n-butyl isocyanate, and the mixture was refluxed until solution was complete. After filtering and evaporating to near dryness it was diluted with petroleum ether to precipitate the product which was recrystallized from 30 mL of EtOH by addition of H_2O to give 400 mg (24%), mp 129–130 °C.

2-Phenyl-3-[3,4-(methylenedioxy)phenyl]imidazo[4,5-*b*]pyridine (I-75). A mixture of 1.15 g (0.005 mol) of 2-[3,4-(methylenedioxy)phenyl]-3-aminopyridine and 600 mg (0.005 mol) of benzoic acid was added to 20 mL of $POCl_3$. The mixture was stirred and refluxed for 2 h. The excess of $POCl_3$ was removed in vacuo and the dark residue treated with ice and $NaHCO_3$. The resulting solid was extracted with warm benzene. Petroleum ether was added to the cloud point and the mixture filtered through Super cel. The filtrate with more petroleum ether gave a gum which crystallized. It was recrystallized from 2 mL of hot benzene by the addition of 10 mL of ether. The yield was 100 mg (6%), mp 154–155 °C.

1-Allyl-1,3-dihydro-3-[3,4-(methylenedioxy)phenyl]-2-oxoimidazo[4,5-*b*]pyridinium Methiodide (I-97). A solution of 500 mg of I-21 and 3 mL of MeI in 50 mL of acetone was refluxed for 2 h when another 3 mL of MeI was added and refluxing was continued for another 2 h. The solution was concentrated to a small volume and ether was added to crystallize the quaternary salt. There was obtained 450 mg which was recrystallized from acetone–ether giving 300 mg (41%) melting at 202–203 °C.

3-(2-Hydroxyphenyl)-1,2,3-triazolo[4,5-*b*]pyridine (T-148). A mixture of 1.2 g of T-140, 12.5 g of AlC_3, and 175 mL of dry C_6H_6 was refluxed 16 h. The cooled mixture was stirred into ice–water containing 5 mL of concentrated HCl. The C_6H_6 layer was separated, washed with H_2O and $NaHCO_3$ solution, dried, and evaporated to dryness. The residue was recrystallized from C_6H_6 to give 500 mg (44%), mp 165–166 °C.

2-(2-Fluoroanilino)-3-amino-5-nitropyridine. A mixture of 2.4 g (0.0085 mol) of N-67, 45 mL of EtOH, and 15 mL of NH_4OH was heated to 70 °C with stirring and H_2S bubbled in for 15 min. Upon cooling, 1.4 g of solid separated. This was crystallized from 10 mL of EtOH to give 600 mg (28%), mp 171–172 °C. Anal. ($C_{11}H_9FN_4O_2$) C, H, N.

Acknowledgment. The authors are indebted to Dr. C. Gordon Van Arman, Edwin A. Risley, and George C. Beveridge for the antiinflammatory results, to the analytical laboratories for their service, and to Dr. Peter Gund for the structure–activity study.

References and Notes

(1) B. E. Witzel, T. Y. Shen, P. M. Graham, R. L. Clark, and A. A. Pessolano, U.S. Patent 3 654 291 (1972), 3 721 676 (1973); B. E. Witzel, U.S. Patent 3 754 088 (1973); B. E. Witzel, C. P. Dorn, and T. Y. Shen, U.S. Patent 3 715 358 (1973); A. A. Pessolano, B. E. Witzel, P. M. Graham, R. L. Clark, and T. Y. Shen, U.S. Patent 3 821 201 (1974); T. Y. Shen and R. L. Clark, U.S. Patent 3 845 065 (1974); T. Y. Shen, R. L. Clark, A. A. Pessolano, B. E. Witzel, and T. J. Lanza, U.S. Patent 4 038 396 (1977).

(2) K. F. Swingle in "Medicinal Chemistry: A Series of Monographs", G. DeStevens, Ed., Vol. 13, "Anti-Inflammatory Agents", Vol. II, R. A. Scherrer and M. W. Whitehouse, Ed., Academic Press, New York, N.Y., 1974, p 58.

(3) T. Y. Shen in ref 2, Vol. I, 1974, p 182.

(4) M. M. Robinson, U.S. Patent 3 719 683 (1973).

(5) J. R. Vaughan, Jr., U.S. Patent 2 637 731 (1953).

(6) H. F. W. Rochling, K. H. Buchel, and F. W. A. G. K. Korte, U.S. Patent 3 459 759 (1969).

(7) W. vonBebenburg, U.S. Patent 3 819 640 (1974).

(8) (a) M. Israel and A. R. Day, *J. Org. Chem.*, **24**, 1455 (1959); (b) M. Israel, L. C. Jones, and E. J. Modest, *Tetrahedron*

Lett., **46**, 4811 (1968); (c) A. Nowajski, *Rocz. Chem.*, **43**, 573 (1969); *Chem. Abstr.*, **70**, 115142 (1969).
(9) J. Elks, G. I. Gregory, J. D. Cocker, L. Stephenson, and W. K. Warburton, British Patent 1 268 772 (1972).
(10) I. J. Pachter and M. C. Kloetzel, *J. Am. Chem. Soc.*, **74**, 1321 (1952).
(11) (a) C. A. Winter and L. Flataker, *J. Pharmacol. Exp. Ther.*, **150**, 165 (1965); (b) N. B. Eddy and D. Leimbach, *ibid.*, **107**, 385 (1953); (c) F. Haffner, *Dtsch. Med. Wochenschr.*, **55**, 731 (1929).
(12) (a) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 545 (1962); (b) C. A. Winter and G. W. Nuss, *Arthritis Rheum.*, **9**, 394 (1966); (c) B. B. Newbould, *Br. J. Pharmacol.*, **24**, 632 (1965).
(13) C. D. Johnson, A. R. Katritsky, B. J. Ridgewell, and M. Viney, *J. Chem. Soc.*, 1204 (1967).
(14) T. Takahashi and Y. Yamamoto, *J. Pharm. Soc. Jpn.*, **69**, 409 (1949); *Chem. Abstr.*, **44**, 1977 (1950).
(15) A. H. Berrie, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 2042 (1952).
(16) J. H. Boyer and W. Schoen, *J. Am. Chem. Soc.*, **78**, 423 (1956).
(17) A. H. Berrie, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 2590 (1951).
(18) N. Whittaker, *J. Chem. Soc.*, 1565 (1951).
(19) B. R. Pai, S. Prabhakar, P. S. Santhanam, M. Seetha, and V. Sundarsanam, *Indian J. Chem.*, **2** (11), 449 (1964).
(20) P. M. Heertjes and E. A. M. F. Dahmen, *Recl. Trav. Chim. Pays-Bas*, **62**, 620 (1943).
(21) J. Boeseken and G. Slooff, *Proc. Acad. Sci. Amsterdam*, **35**, 1250 (1932); *Chem. Abstr.*, **27**, 3457 (1933).
(22) Y. Kawase, S. Takata, and E. Hikishima, *Bull. Chem. Soc. Jpn.*, **44**, 749 (1971); *Chem. Abstr.*, **74**, 141422d (1971).
(23) Hoffmann-La Roche, British Patent 1 276 966 (1972).
(24) R. R. Bishop, E. A. S. Cavell, and N. B. Chapman, *J. Chem. Soc.*, 437 (1952).

Effects of Thiophene Analogues of Chloroamphetamines on Central Serotonergic Mechanisms

S. Conde, R. Madroñero,*

Department of Chemistry

M. P. Fernández-Tomé, and J. del Río

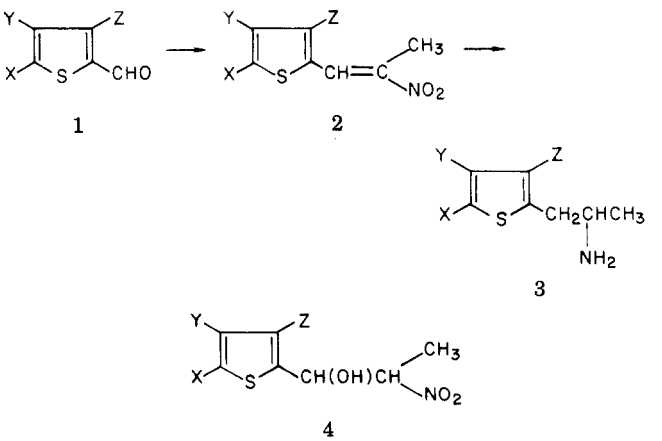
Department of Pharmacology, Instituto de Química Médica, Juan de la Cierva-3, Madrid-6, Spain. *Received March 20, 1978*

Ring-chlorinated thienylisopropylamines, thiophene analogues of chloroamphetamines, have been synthesized and their effects on serotonergic mechanisms in the rat brain have been evaluated. With 4,5-dichlorothienylisopropylamine (**3e**), a pharmacological profile similar to that of *p*-chloroamphetamine, consisting in a marked and long-lasting serotonin depletion and a rather strong and prolonged inhibition of synaptosomal uptake of serotonin, was found. Chloro substitution in position C_3 of the thiophene ring did not determine brain serotonin depletion nor serotonin uptake inhibition but enhanced brain MAO inhibitory activity present in all these compounds. 3,5-Dichlorothienylisopropylamine (**3g**) was the only compound of the series in which the inhibition of serotonin uptake was more marked than the serotonin depleting property.

Ring-halogenated amphetamines affect predominantly brain serotonin (5-HT) metabolism.[1] *p*-Chloroamphetamine (PCA) has been extensively studied in this regard, and it is known that this drug exerts multiple actions on 5-HT metabolism. PCA inhibits tryptophan hydroxylase,[2] releases serotonin from storage granules,[3,4] blocks serotonin reuptake into the serotonergic neurons,[4] and inhibits 5-HT metabolism by monoamine oxidase (MAO).[5] After treatment of rats with a high enough dose of PCA, some of the effects of this drug become irreversible. Thus, brain levels of 5-HT are markedly reduced for several months and the 5-HT synaptosomal uptake system shows also a long-term inhibition.[6] The selective neurotoxic actions of PCA on 5-HT neurons in the brain may result from the formation of a neurotoxic metabolite or from the prolonged permanence of the drug inside the neuron.[7] In any case, the continual uptake of PCA into the 5-HT neurons seems necessary to obtain neuronal destruction.[8] This continual uptake of PCA is possible due to the long half-life of this drug in the organism.[9] Human studies have shown that PCA, like other blockers of 5-HT reuptake, is an effective antidepressant.[10] However, the possibility of a toxic destruction of 5-HT neurons has perhaps prevented more extensive trials with this drug in psychiatry.

Fuller and Molloy[11] suggested that the multiple actions of PCA were potentially dissociable and, in fact, some PCA analogues which only retain some pharmacological features of the parent drug have already been developed.[12,13] With this aim, we have prepared some ring-chlorinated thienylisopropylamines, thiophene analogues of chloroamphetamines, and have studied their effects on some aspects of brain 5-HT dynamics. The bioisosteric equivalence of the benzene and thiophene rings is well known,[14] and we have recently found in our laboratory new examples of this bioequivalence.[15-17] On the other hand, the substitution of benzene by thiophene could perhaps lead in the present case to chloroamphetamines analogues more easily metabolized in the brain and, in consequence,

Scheme I



1 2 3 4

0022-2623/78/1821-0978$01.00/0 © 1978 American Chemical Society