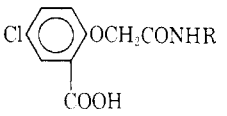
TABLE IV
PHYSICAL PROPERTIES OF



No.[a]	R	Yield, %	Mp, °C dec	Formula
4	*m*-$C_6H_4NHCONHC_6H_4SO_2F$-*p*	63[b]	245–247	$C_{22}H_{17}ClFN_3O_7S$
5	*m*-$C_6H_4NHCONHC_6H_3$-2-Cl-5-SO_2F	65[c,d]	268–270	$C_{22}H_{16}Cl_2FN_3O_7S$
6	*m*-$C_6H_4NHCONHC_6H_3$-4-Me-3-SO_2F	62[b,e]	255–257	$C_{23}H_{19}ClFN_3O_7S$
7	*m*-$CH_2C_6H_4NHCONHC_6H_4SO_2F$-*m*	73[e]	225–227	$C_{23}H_{19}ClFN_3O_7S$
8	*m*-$CH_2C_6H_4NHCONHC_6H_4SO_2F$-*p*	78[d,e]	230–232	$C_{23}H_{19}ClFN_3O_7S$
9	*p*-$CH_2C_6H_4NHCONHC_6H_4SO_2F$-*m*	72[b,c,f]	227–229	$C_{23}H_{19}ClFN_3O_7S$
10	*p*-$CH_2C_6H_4NHCONHC_6H_4SO_2F$-*p*	73[f]	231–234	$C_{23}H_{19}ClFN_3O_7S$
11	*m*-$CH_2C_6H_4NHCONHC_6H_3$-4-Me-3-SO_2F	87[b]	238–241	$C_{24}H_{21}ClFN_3O_7S$
12	*m*-$CH_2C_6H_4NHCONHC_6H_3$-2-Cl-5-SO_2F	51[b]	232–234	$C_{23}H_{18}Cl_2FN_3O_7S$
13	*m*-$CH_2C_6H_4NHCONHC_6H_3$-3-Cl-4-SO_2F	35[c,d]	227–229	$C_{23}H_{18}Cl_2FN_3O_7S$
14	*p*-$CH_2C_6H_4NHCONHC_6H_3$-4-Me-3-SO_2F	80[c,d]	186–220	$C_{24}H_{21}ClFN_3O_7S$
15	*p*-$CH_2C_6H_4NHCONHC_6H_3$-2-Cl-5-SO_2F	71[c,e]	229–231	$C_{23}H_{18}Cl_2FN_3O_7S$

[a] All prepared by method A and analyzed for C, H, and F; each moved as a single spot on polyamide MN. [b] Precipitated from MeOEtOH with H_2O, then washed with hot EtOH and hot acetone. [c] Reprecipitated from MeOEtOH with H_2O. [d] Recrystallized from Me_2CO–H_2O. [e] Recrystallized from EtOH. [f] Recrystallized from MeOH.

temperature. The mixture was spin evaporated *in vacuo*. The residue was crystallized from DMF–H_2O, then MeOEtOH; yield 11.9 g (63%) of white needles, mp 182–184°. *Anal.* ($C_{17}H_{15}ClN_2O_6$) C, H, N.

2-Carboxy-4-chloro-N-[*m*-(3-fluorosulfonyl-4-methylphenylureido)benzyl]phenoxyacetamide (11) (Method A).—A solution of 371 mg (1 mmole) of **44**, 354 mg (1 mmole) of O-(*p*-nitrophenyl) N-(3-fluorosulfonyl-4-methylphenyl)carbamate (**36**),[20] and 100 mg (1.3 mmoles) of pyridine in 5 ml of DMF was allowed to stand for 12 hr, then diluted with 20 ml of 5% HCl. The product was collected on a filter and washed with H_2O, Me_2CO, and hot EtOH. The product was reprecipitated from MeOEtOH with H_2O, then washed again with hot EtOH; yield 480 mg (87%) of white powder, mp 238–241° dec, negative Bratton–Marshall test for aromatic amine.[21] See Table IV for additional data and compounds prepared by this method.

(20) Prepared in this laboratory by W. F. Wood by the previously described general method.[18]

(21) B. R. Baker, D. V. Santi, J. K. Coward, H. S. Shapiro, and J. H. Jordaan, *J. Heterocycl. Chem.*, **3**, 425 (1966).

Derivatives of Imidazole. III. Synthesis and Pharmacological Activities of Nitriles, Amides, and Carboxylic Acid Derivatives of Imidazo[1,2-*a*]pyridine

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A number of improved laboratory procedures for the synthesis of imidazo[1,2-*a*]pyridine derivatives are reported. The resulting compounds, which are structurally related to indole derivatives, have been screened for analgetic, antipyretic, anticonvulsant, and antiinflammatory activity. Phytopharmacological tests have also been performed on the derivatives structurally related to indoleacetic acid.

Previous publications from this laboratory[2-4] described some aspects of the chemistry of imidazo[1,2-*a*]pyridines and showed that these and related compounds react easily with electrophilic reagents, similarly to indole, in the 3 position. π-Electron density calculations[5] for imidazo[1,2-*a*]pyridines further confirmed that electrophilic substitution (on carbon) should occur at the 3 position; other chemical similarities between imidazo[1,2-*a*]pyridines and indole derivatives were recently shown.[6-9]

In accord with a continuing program designed for the pharmacological screening of new imidazo[1,2-*a*]pyridines, we thought it would be interesting to synthesize and test a number of derivatives that may be considered analogs of indoleacetic acid and indomethacin.[10]

Pharmacological tests on the analgetic, antiinflammatory, antipyretic, and muscle relaxant activity were

(1) To whom all inquiries concerning pharmacology should be sent.

(2) L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Biancotti, A. Gamba, and W. Murmann, *J. Med. Chem.*, **8**, 305 (1965).

(3) L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Gamba, A. Olivi, and W. Murmann, *ibid.*, **9**, 29 (1966).

(4) L. Almirante, A. Mugnaini, L. Polo, and E. Provinciali, *Boll. Chim. Farm.*, **105**, 32 (1966).

(5) W. W. Paudler and H. L. Blewitt, *Tetrahedron*, **21**, 353 (1965); *J. Org. Chem.*, **30**, 4081 (1965); **31**, 1295 (1966); W. W. Paudler, J. E. Kudez, and L. S. Helmick, *ibid.*, **33**, 1379 (1968).

(6) J. G. Lombardino, *ibid.*, **30**, 2403 (1965).

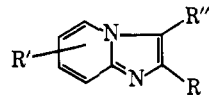
(7) J. P. Paolini and R. K. Robins, *J. Heterocycl. Chem.*, **2**, 53 (1965); *J. Org. Chem.*, **30**, 4085 (1965).

(8) L. Pentimelli and S. Bozzini, *Boll. Sci. Fac. Chim. Ind. Bologna*, **23**, 173, 181 (1965); *Chem. Abstr.*, **63**, 14848*b,f* (1965).

(9) C. K. Bradsher, E. F. Litzinger, Jr., and M. F. Zinn, *J. Heterocycl. Chem.*, **2**, 331 (1965).

(10) C. A. Winter, E. A. Risley, and G. W. Nuss, *Federation Proc.*, **22**, 543 (1963).

TABLE I



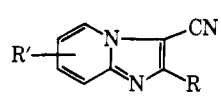
No.	R	R′	R″	Method	% yield	Recrystn solvent	Mp, °C	Formula[i]
1[a]	H	H	CN	B	90.5	*i*-PrOH	156–157	$C_8H_5N_3$
2[b]	H	7-CH_3	CN	B	92	C_6H_6	161–162	$C_9H_7N_3$
3	CH_3	H	CN	A	65	H_2O	115–116	$C_9H_7N_3$
4	*p*-ClC_6H_4	H	CN	A	57	EtOH	193–194	$C_{14}H_8ClN_3$
5	$C_6H_4SO_2CH_3$-*p*	H	CN	A	60	DMF	278–279	$C_{15}H_{11}N_3O_2S$
6	H	H	CH_2CN	D	51	THF	145–146	$C_9H_7N_3$
7	H	7-CH_3	CH_2CN	D	67	H_2O	154–155	$C_{10}H_9N_3$
8	CH_3	H	CH_2CN	B	60	C_6H_6	157–158	$C_{10}H_9N_3$
				D	70			
9[c]	*p*-ClC_6H_4	H	CH_2CN	D	44	MeOH	149–150	$C_{15}H_{10}ClN_3$
10[d]	$C_6H_4SO_2CH_3$-*p*	H	CH_2CN	B	78	MeOH	215–217	$C_{16}H_{13}N_3O_2S$
11[a,e]	H	H	$CONH_2$	A	85	*i*-PrOH	252–254 dec	$C_8H_7N_3O$
12	H	7-CH_3	$CONH_2$	A	80	EtOH	295–296 dec	$C_9H_9N_3O$
13	CH_3	H	$CONH_2$	A	22	MeOH	195–196	$C_9H_9N_3O$
14	*p*-ClC_6H_4	H	$CONH_2$	C	96.5	DMF	257–258	$C_{14}H_{10}ClN_3O$
15	$C_6H_4SO_2CH_3$-*p*	H	$CONH_2$	C	83	DMF	304–306	$C_{15}H_{13}N_3O_3S$
16	H	H	CH_2CONH_2	F	51.8	MeOH	217–218	$C_9H_9N_3O$
17	H	7-CH_3	CH_2CONH_2	E	52	H_2O	192–193	$C_{10}H_{11}N_3O$
18	CH_3	H	CH_2CONH_2	E	73	H_2O	229–230	$C_{10}H_{11}N_3O$
19[f]	*p*-ClC_6H_4	H	CH_2CONH_2	E	71	MeOH	263–265	$C_{15}H_{12}ClN_3O$
				C	84.5			
20[d]	$C_6H_4SO_2CH_3$-*p*	H	CH_2CONH_2	E	86	MeOH	271–272	$C_{16}H_{15}N_3O_3S$
21[a]	H	H	COOH	G	93	H_2O	244–245 dec	$C_8H_6N_2O_2$
22	H	7-CH_3	COOH	G	93	DMF	214–215 dec	$C_9H_8N_2O_2$
23	CH_3	H	COOH	G	63	DMF	182–183 dec	$C_9H_8N_2O_2$
24[g]	$C_6H_4SO_2CH_3$-*p*	H	COOH	G	83	DMF	212–213 dec	$C_{15}H_{12}N_2O_4S$
25	H	H	CH_2COOH	E	53	EtOH	258–259 dec	$C_9H_8N_2O_2$
				G	76			
26	H	7-CH_3	CH_2COOH	G	57	30% EtOH	266–267 dec	$C_{10}H_{10}N_2O_2$
27	CH_3	H	CH_2COOH	G	61	Me_2CO	247 dec	$C_{10}H_{10}N_2O_2$
				H	57.3	EtOH		
28	CH_3	5-CH_3	CH_2COOH	H	34	H_2O	314 dec	$C_{11}H_{12}N_2O_2$
29	CH_3	7-CH_3	CH_2COOH	H	29.4	EtOH–H_2O	271–272	$C_{11}H_{12}N_2O_2$
30	*p*-ClC_6H_4	H	CH_2COOH	G	75	EtOH–H_2O	256–257 dec	$C_{15}H_{11}ClN_2O_2$
31[d,h]	$C_6H_4SO_2CH_3$-*p*	H	CH_2COOH	G	70	10% HCl	318–319 dec	$C_{16}H_{15}ClN_2O_4S$

[a] This compound was also synthesized by another method by J. Mandereau, P. Reynaud, and R. Moreau, *Compt. Rend.*, **257**, 3434 (1963); see also ref 4. [b] Hydrochloride mp 252–253°. [c] Hydrochloride mp 299–300°. [d] See the first paper of this series.[2] [e] Hydrochloride mp 298–299°; perchlorate mp 257–259°. [f] Hydrochloride mp 301–302°; hydrogen maleate mp 197–198°. [g] This compound loses CO_2 at 212–213° and melts at 242–243° like the 2-(4-methylsulfonylphenyl)imidazo[1,2-*a*]pyridine. [h] As HCl salt. [i] All compounds were analyzed for C, H, N.

performed and the results compared with those obtained with 2-(4-methylsulfonylphenyl)imidazo[1,2-*a*]-pyridine hydrochloride which was the most promising compound we studied[2] in this series.

Phytopharmacological tests were extended on the derivatives structurally related to indoleacetic acid.

Chemistry.—Unsuccessful attempts to prepare the nitriles (Table I, **1–5**) by treating the corresponding

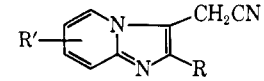


3-bromoimidazo[1,2-*a*]pyridines with alkaline or cuprous cyanides led us to investigate a one-step conversion of aldehydes into nitriles.[11]

The 3-formylimidazo[1,2-*a*]pyridines were prepared with the Vilsmeier reagent[4] and treated with $HONH_3^+Cl^-$, sodium formate, and 99% HCO_2H. In all the cases considered, this method led predominantly to the nitriles or to corresponding amides, both contaminated by the oxime of the starting aldehyde. The purification of these mixtures was easily followed by thin layer chromatography, since imidazo[1,2-*a*]pyridines are strongly fluorescent to uv light.

The nitriles **3–5** and the amides **11–13** were isolated directly by the above method; the nitriles **1**, **2** were prepared from the corresponding amides **11**, **12** by treatment with $POCl_3$, whereas the amides **14**, **15** were obtained by warming the nitriles **4**, **5** in 96% H_2SO_4.

The nitriles (Table I, **6–10**) were synthesized from the methiodides of the corresponding Mannich bases[4] and CN^- in absolute EtOH.



The reaction of the dimethylamino Mannich base of the imidazo[1,2-*a*]pyridine, its 2-methyl analog, and the corresponding methiodide, with CN^- was tried unsuccessfully by Lombardino[6] in EtOH, H_2O, or DMSO; he found that with increasingly severe conditions only substantial quantities of the starting material could be recovered. Our results confirm that the Man-

(11) T. Van Es, *J. Chem. Soc.*, 1564 (1965).

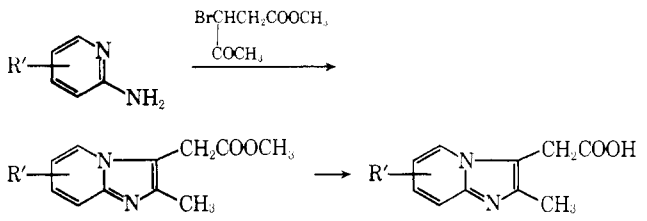
nich bases of imidazo[1,2-*a*]pyridines do not react like gramine[12] but, when the corresponding methiodides were used, the reaction with CN^- led to the nitriles, under anhydrous conditions, and to mixtures of related nitriles, amides, and carboxylic acids when the solvent was aqueous.

From these mixtures the amides **17**–**20** could be easily isolated and purified; the amide **16** was prepared by melting the corresponding carboxylic acid **25** with urea, which was the only compound we were able to isolate when the methiodide of 2-dimethylaminomethylimidazo[1,2-*a*]pyridine was refluxed in H_2O with CN^-.

The carboxylic acids **21**–**31** were obtained by hydrolyzing in alkaline medium the corresponding nitriles or amides.

Another method used for preparing acids **27**–**29** was to condense 2-aminopyridine or 2-aminopicolines with methyl bromolevulinate and hydrolyze the esters obtained as shown in Scheme I.

SCHEME I



The nmr spectrum of the 3-carboxymethylimidazo-[1,2-*a*]pyridine (Table I, **25**), the analog of indoleacetic acid, clearly supported the strong aromaticity of the molecule. The ir spectrum confirmed the presence of CO_2H. Physical properties, formulas, and yields of the synthesized compounds are reported in Table I.

Pharmacological Studies.—LD_{50} values in mice were determined, and analgetic, antiinflammatory, antipyretic, and anticonvulsant activities were investigated in basic screening procedures as previously described.[2,3] The pharmacological results are presented in Table II in comparison with the most active compound [2-(4-methylsulfonylphenyl)imidazo[1,2-*a*]pyridine, **32**] of the earlier series.

Only the nitriles, **1**–**3** displayed significant analgetic activity; all three compounds are central depressants, the CH_3 side chain increasing this central effect and consequently the analgetic and anticonvulsant activity.

Among the compounds most closely related to indomethacin, only amide **19** showed considerable antipyretic and hypothermal activity. The corresponding nitrile **9** and the carboxylic acid **30** were less active. Amide **19** was the only compound that showed marked activity against electroshock convulsions and convulsions or death from pentylenetetrazole. It possessed no activity against strychnine-induced convulsions.

The antiinflammatory activity of amide **19** was significantly high and of the same order as that of **32**. These two compounds were less active than indomethacin as antiinflammatory agents but showed an interesting spectrum and degree of activity as potential therapeutic agents.

Phytopharmacological Studies.—A number of the compounds described were studied, under a cooperation agreement, by the Olefins Division of Union Carbide, in a very extended screening of phytopharmacological activities. None of the compounds showed any significant activity.

General Comments.—The introduction in the molecule of imidazo[1,2-*a*]pyridines of a substituent in 3 position, such as CN or CH_2CN, $CONH_2$ or CH_2CONH_2, COOH or CH_2COOH, generally lowered the pharmacodynamic activity of these compounds. Only amide **19** showed a spectrum and degree of activity comparable to that of the most interesting compound we found in this series (**32**).[2]

Experimental Section[13]

2-Methyl-3-cyanoimidazo[1,2-*a*]pyridine (3). Method A. A mixture of 30 g (0.187 mole) of 2-methyl-3-formylimidazo-[1,2-*a*]pyridine, 16.3 g (0.235 mole) of $NH_2OH \cdot HCl$, and 23 g (0.338 mole) of HCO_2Na in 300 ml of 99% HCO_2H was refluxed for 3 hr. The solution was evaporated under vacuum and the residue, dissolved in 100 ml of H_2O, was neutralized at pH 7 with Na_2CO_3. The precipitated solid was filtered, dried, and refluxed with 100 ml of C_6H_6. The undissolved material was the oxime of the starting aldehyde (2 g). C_6H_6 was removed under vacuum and the residue, after crystallizing twice from H_2O, gave 19.1 g (65%) of **3**. Compounds **4** and **5** were prepared analogously. After refluxing for 3 hr, the solutions obtained were evaporated and the residues were taken up in H_2O and alkalized to pH 9 with Na_2CO_3. In both cases a solid was filtered, dried, and refluxed with CH_2Cl_2. The oximes of the starting aldehydes were filtered and the CH_2Cl_2 was removed under vacuum. The residue, after crystallizing, respectively, from EtOH and DMF, gave **4** (57%) and **5** (60%).

3-Carboxamidoimidazo[1,2-*a*]pyridine (11). Method A. A mixture of 66 g (0.452 mole) of 3-formylimidazo[1,2-*a*]pyridine, 39.5 g (0.572 mole) of $NH_2OH \cdot HCl$, and 56 g of HCO_2Na in 500 ml of 99% HCO_2H was refluxed under stirring, for 3 hr. After evaporating the solution under vacuum, the residue was taken up in 500 ml of H_2O, decolorized with charcoal, filtered, and alkalized with Na_2CO_3. The obtained solid was crystallized from *i*-PrOH and gave 62 g (85%) of **11**. Compound **12** was prepared by the same procedure.

2-Methyl-3-carboxamidoimidazo[1,2-*a*]pyridine (13). Method A.—Compound **13** could be obtained from the mother liquor of the crystallization of the 2-methyl-3-cyanoimidazo[1,2-*a*]-pyridine (**3**) by evaporating under vacuum and by twice recrystallizing the residue from MeOH (yield 22%). By increasing the reflux time of the aldehyde with $NH_2OH \cdot HCl$ and HCO_2Na to 10 hr, the reaction mixture contained a larger quantity of the oxime and of the amide **13**. By treating the above reagents in 70% HCO_2H, only the oxime of the starting aldehyde could be recovered.

3-Cyanoimidazo[1,2-*a*]pyridine (1). Method B.—A suspension of 62 g (0.385 mole) of 3-carboxamidoimidazo[1,2-*a*]pyridine (**11**) in 500 ml of $POCl_3$ was refluxed for 16 hr. The excess of $POCl_3$ was removed from the dark solution under vacuum, and the residue was dissolved in 750 ml of H_2O, decolorized with charcoal, alkalized with 25% NH_4OH, and extracted ($CHCl_3$, 800 ml). The solvent was decolorized, dried, and evaporated under vacuum. The solid residue was taken up in 350 ml of H_2O and dissolved in 50 ml of 37% HCl. To the decolorized acid solution, 25% NH_4OH was added and the pH was adjusted to 6.5–7. After chilling, **1** (49.7 g, 90.5%) was filtered and recrystallized from *i*-PrOH. Compounds **2**, **8**, and **10** were synthesized by the same procedure.

2-(4-Chlorophenyl)-3-carboxamidoimidazo[1,2-*a*]pyridine (14). Method C.—A solution of 14 g (0.550 mole) of 2-(4-chlorophenyl)-3-cyanoimidazo[1,2-*a*]pyridine (**4**) in 70 ml of 96% H_2SO_4 was heated and stirred at 90° for 1 hr. After cooling in ice, the solution was diluted to 1 l. with H_2O and alkalized with 25% NH_4OH. The obtained solid (14.5 g, 96.5%) was recrystallized

(12) H. R. Snyder and F. J. Pilgrim, *J. Am. Chem. Soc.*, **70**, 3770 (1948).

(13) All melting points were taken in a capillary apparatus and were corrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

TABLE II

PHARMACOLOGICAL ACTIVITIES OF DERIVATIVES OF IMIDAZOLE

No.	Randall and Selitto[a] Inflamed foot	Randall and Selitto[a] Control foot	Analgetic act. Hot plate[b]	Analgetic act. Electric stimulus[b]	Analgetic act. Tail clip[c]	Analgetic act. Phenylquinone[d]	Antiinflam act. rat foot edema[e] Yeast	Antiinflam act. rat foot edema[e] Carrageenan	Antipyretic act. index[f] po	Antipyretic act. index[f] ip	Hypothermal act. index[g] po	Hypothermal act. index[g] ip	Anticonvulsant act. Electroshock[h] convulsions	Anticonvulsant act. Pentylenetetrazole[h] Convulsions	Anticonvulsant act. Pentylenetetrazole[h] Death	Anticonvulsant act. Strychnine[i] Convulsions	Anticonvulsant act. Strychnine[i] Death	Acute toxicity[j] Estd LD_{50}, mg/kg ip (mouse)	Acute toxicity[j] Gross behavioral changes
1	173	152	0	42	60	70	41	64	6.0		12.0		0	0	0	0	0	400	*o, p, r, u*
2	194	187	53	95	100	30	42	34	2.0		12.6		100	50	0	0	0	600	*l, m, o, p, r, u*
3	189	167	49	0	70	20	67	45	2.6		15.1		20	11	0	0	0	600	*o, p, r, u*
4	15	0	0	0	30	30	0	0	2.3		−2.0		0	0	0			>3000	*q*
5	39	12	23	0	40	20	0	0	−1.7		−4.0		0	0	0	0	0	>3000	*k*
6	0	0	−11	−37	80	0	0	0	2.0	8.6	−0.1	−0.9	0	0	0	0	0	40	*n, p*
7	0	0	0	0	80	67	0	35	1.8	5.9	3.9	−0.2	0	0	0	0	0	60	*m, p, r*
8	0	0	0	0	40	30	0	26	1.6	4.3	0.4	0.7	0	0	0	20	20	40	*l, n, p*
9	78	98	55	0	0	56	8	51	4.5	27.3	15.0	10.5	25	50	33	0	0	600	*p, t, u*
10	19	0	23	0	25	40	30	22		4.7		−1.9	0	0	0	0	0	>3000	*k*
11	52	17	25	0	0	0	29	0	3.2		6.0		0	0	0	0	0	180	*k*
12	29	10	0	0	0	20	49	30	8.5		7.8		0	0	0	10	33	500	*p, r, t, u*
13	0	12	21	43	0	0	37	22	9.0		8.3		0	0	0	0	0	500	*t*
14	16	14	0	0	0	0	0	0	−1.9		4.1		0	0	0	0	0	600	*q*
15	−26	−13	27	0	25	20	0	0	−2.4		−2.0		0	0	0	0	0	>3000	*k, q*
16			0	37	30	22		0			0.2		0	0	0	40	33	1400	*p, q*
17	0	0	0	0	20	33	0	0	4.1	5.7	1.0	0.1	0	0	0	0	0	600	*k*
18	64	18	0	0	30	44	29			11.8		0.4	−25	0	0	0	0	2000	*l, n*
19	98	36	37	15	70	78	54	68	19.6	33.1	21.6	28.2	56	90	89	0	0	600	*m, r, t, u*
20	28	20	0	0	0	50	0	0	0.6	7.6		4.0	0	0	0	0	0	2500	*k*
21	85	31	13	78	0	0	11	0	−0.2		3.5		10	10	20	70	20	2000	*p, q*
22	82	47	0	50	0	0	0	30	0.7		1.1		0	0	0	40	0	600	*q*
23	0	20	0	20	0	0	44	0	1.8		−0.9		0	0	0	20	10	600	*l, n, q*
24	−16	−4	−6	−5	50	30	0	21	0.1		2.7		0	0	0			>3000	*k, q*
25	17	11	0	0	0	0	0	0		3.0	−2.7	2.8	22	0	0	0	0	2500	*p*
26	0	0	0	0	40	56	0			0.5		0.4	0	0	0	0	0	>3000	*l, p*
27	0	0	26	0	0	78	25	0	−0.9	3.7		3.2	0	0	0	0	0	2000	*p*
28	0	0	0	0	0	0	0			5.7		−1.4	0	0	0	0	0	2500	*l*
29	0	0	62	0	40	0	0	0	−0.4	5.9	−2.0	−1.7	0	0	0	0	0	>3000	*l*
30	15	0	−62	0	0	44	9	48	2.3	33.6	9.0	4.3	0	60	56	0	0	1200	*l, p, t, u*
31	0	0	0	0	0	70	0	0	0.9	2.5		−1.8	0	0	0	0	0	>3000	*l, p*
32[v]	133	40	55	38	40	65	51	50	16.2	19.5	10.6	12.7	44	28	10	86	92	780	*k, o, s, t*

[a] % increase of pain threshold at $0.25LD_{50}$ (rat) *po*. [b] % increase of pain threshold at $0.33LD_{50}$ (mouse) ip. [c] % of animals insensitive at $0.33LD_{50}$ (mouse) ip. [d] % of animals insensitive at $0.50LD_{50}$ (mouse) *po*. [e] % edema inhibition at $0.25LD_{50}$ (rat) *po*. [f] Amount of reduction of fever in degrees, compared with controls, caused by $0.25LD_{50}$ (rat) *po* or ip in a 6-hr period after treatment (six determinations). [g] Amount of reduction in temperature in degrees compared with controls, caused by $0.25LD_{50}$ (rat) *po* or ip in a 6-hr period after treatment (six determinations). [h] % protection at $0.33LD_{50}$ (mouse) ip. [i] % protection at $0.50LD_{50}$ (mouse) ip. [j] Approximate LD_{50}/168-hr were determined by intraperitoneal administration to groups of five NMRI mice. Observations of the effects of these compounds on behavior were carried out simultaneously with the determination of toxicity. In all tests, the highest dose employed of a compound having low toxicity was 500 mg/kg. [k] Sedation, tranquilization. [l] Irritability. [m] Tremors. [n] Clonic convulsions. [o] Salivation. [p] Depression. [q] Writhing. [r] ↓ muscle tone. [s] Hyperpnea. [t] Hypnosis. [u] Hypothermia. [v] **32** = 2-(*p*-methylsulfonylphenyl)imidazo[1,2-*a*]pyridine hydrochloride.

(DMF). Compounds **15** and **19** were prepared by the same method.

3-Cyanomethylimidazo[1,2-*a*]pyridine (6). Method D.—The methiodide of the 3-dimethylaminomethylimidazo[1,2-*a*]pyridine[4] (83.7 g, 0.26 mole) was dissolved in 500 ml of EtOH, previously dried with $NaBH_4$, NaCN (38.9 g, 0.8 mole) was added, and the mixture refluxed for 16 hr. After filtering, the EtOH was removed under vacuum and the residue was taken up in H_2O (250 ml) and extracted (CH_2Cl_2, 1500 ml). The solvent was decolorized and evaporated. The residue was crystallized (C_6H_6) collecting a first crop (11 g). The filtrate was percolated through alumina and concentrated to about one-third volume. A second crop was collected (10 g), yield 51%. Compounds **7–9** were synthesized by the same procedure.

2-Methyl-3-carboxamidomethylimidazo[1,2-*a*]pyridine (18). Method E.—The 2-methyl-3-dimethylaminomethylimidazo-[1,2-*a*]pyridine methiodide[4] (100 g, 0.3 mole) was dissolved in 400 ml of H_2O, treated with 44.6 g (0.9 mole) of NaCN, and refluxed for 3 hr. After cooling, the solution was extracted (CH_2Cl_2) and the solvent was discarded. After 16 hr at 5°, a crystalline solid was filtered and recrystallized from H_2O giving 41 g (73%) of **18**. Compounds **17**, **19**, and **20** were obtained by the same procedure.

(3-Imidazo[1,2-*a*]pyridine)acetic Acid (25). Method E.—A mixture of 9.5 g (0.03 mole) of the 3-dimethylaminomethylimidazo[1,2-*a*]pyridine methiodide and 4.42 g (0.09 mole) of NaCN in 96 ml of H_2O was refluxed for 3 hr; the $N(CH_3)_3$ and NH_3 gas were collected in a 3% solution of H_3BO_3 and titrated with 1 *N* H_2SO_4. The theoretical amount of 60 ml was used. The solution obtained was evaporated under vacuum and the residue was washed (Me_2CO, EtOAc). The solid (6.6 g) was dissolved in 25 ml of H_2O and the pH was adjusted to 6.7 with AcOH. Compound **25** was filtered and recrystallized from 99% EtOH (2.8 g, 53%).

3-Carboxamidomethylimidazo[1,2-*a*]pyridine (16). Method F.—An intimate mixture of 3 g (0.017 mole) of (3-imidazo-[1,2-*a*]pyridine)acetic acid (**25**) and 3 g of urea was melted and heated at 190–195° for 3 hr. After cooling, the residue was washed (5% $NaHCO_3$, cold Me_2CO) and recrystallized (MeOH) (1.5 g, 51.8%).

(2-Methyl-3-imidazo[1,2-*a*]pyridine)acetic Acid (27). Method G.—A solution of 6 g (0.032 mole) of the amide **18** and 15 g of KOH in 30 ml of H_2O and 120 ml of 95% EtOH was refluxed under N_2 for 2 hr. The NH_3 gas was collected in a 5% solution of H_3BO_3 and titrated with 1 *N* H_2SO_4. The solution was evaporated and the residue was dissolved in 40 ml of H_2O and decolorized. The solution was adjusted to pH 7 with AcOH and the precipitated solid was collected, yield 4 g (61%). The above procedure was used to synthesize the carboxylic acids **21**, **22**, and **31** starting from the corresponding amides, and **23–25**, and **30** starting from the nitriles. The acid **26**, which was very soluble in H_2O, could be obtained by hydrolyzing the corresponding nitrile, by percolating the alkaline solution over Amberlite IRC 50 (CO_2H form), and by evaporating the eluate to dryness.

The 2-(4-chlorophenyl)-3-carboxyimidazo[1,2-*a*]pyridine could not be prepared because both alkaline and acidic hydrolysis of the nitrile **4** or of the amide **14** led to extensive decarboxylation; 2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine[14] was the only compound isolated.

2,7-Dimethyl-3-carboxymethylimidazo[1,2-*a*]pyridine (29). Method H.—A solution of 2-amino-4-methylpyridine (21.6 g, 0.2 mole) and methyl 3-bromolevulinate (20.9 g, 0.1 mole) in 99% EtOH (80 ml) was stirred at 60° for 3 hr. The solvent was removed *in vacuo* and the residue, dissolved in H_2O, was alkalized with NaOH and extracted ($CHCl_3$). The aqueous layer was brought to pH 6.7 with AcOH and distilled *in vacuo* until dry. The residue was triturated with H_2O (15 ml) and the solid obtained was filtered and washed with ice–water. The acid **29** was recrystallized from 85% EtOH (36 ml) as a white, hygroscopic crystalline solid (6 g). Compounds **27** and **28** were obtained by the same procedure.

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Spirans. XV. Spirans Derived from 3-Trifluoromethylcyclohexanone[1,2]

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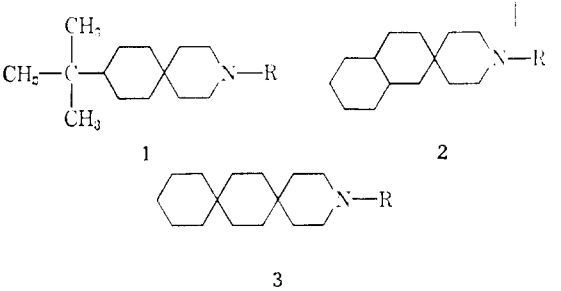
Various spiro[5.4]decane and spiro[5.5]undecane compounds containing a trifluoromethyl substitution in the 7 or 8 position have been synthesized. When evaluated biologically, N-(3-dimethylaminopropyl)-8-trifluoromethyl-3-azaspiro[5.5]undecane showed the best activity and is potentially an interesting anticancer compound.

Molecular modification of a parent compound has long been a tool in the design of safer and more effective synthetic analogs. In numerous cases, the trifluoromethyl group has led to compounds with a more favorable ratio of primary activity to side effects. With this as a basic corollary, we have now evaluated the effect on potency and other reactions of the trifluoromethyl group when introduced in position 8 or 3-azaspiro[5.5]undecane and position 7 of 2-azaspiro[5.4]decane (Table I).

We have been interested in the cytotoxicity of 3-azaspiro[5.5]undecanes and have previously reported on the activity of 9-butyl (**1**),[3] 8,9-cyclotetramethylene (**2**),[4] and 9,9-cyclopentamethylene (**3**)[1,5] derivatives.



All of these compounds have an inhibitory activity in the range of 1 μg/ml or less when tested on the growth

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