# Derivatives of Imidazole. I. Synthesis and Reactions of Imidazo[1,2-a]pyridines with Analgesic, Antiinflammatory, Antipyretic, and Anticonvulsant Activity

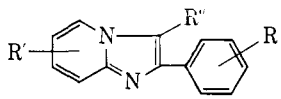
LUIGI ALMIRANTE, LUIGI POLO, ALFONSO MUGNAINI, ERCOLINA PROVINCIALI, PIERLUIGI RUGARLI, ADRIANA BIANCOTTI, AFRO GAMBA, AND WALTER MURMANN[1]

*Research Department, Selvi e C., Laboratorio Bioterapico Milanese, Milan, Italy*

*Received September 29, 1964*

A series of 42 derivatives of imidazo[1,2-*a*]pyridine has been prepared and examined for analgesic, antiinflammatory, antipyretic, and muscle-relaxant activity. The results have been compared with those obtained under same conditions with acetylsalicylic acid, aminopyrine, phenylbutazone, and chlortenoxazine. Several members of the series display high activities in a variety of pharmacological tests, the most interesting being 2-(*p*-methylsulfonylphenyl)imidazo[1,2-*a*]pyridine hydrochloride (**11**) and 2-(*p*-methylsulfonylphenyl)-3-(dimethylaminomethyl)imidazo[1,2-*a*]pyridine dihydrochloride (**22**). The experimental findings suggest that further pharmacological and toxicological investigations of some of these compounds may be of interest for evaluation as therapeutic agents in man.

The antiinflammatory activity of 2-(*p*-nitrophenyl)-imidazo[1,2-*a*]pyridine (I, R'' = R' = H; R = *p*-$NO_2$)[2] has led us to a more thorough and systematic study of the synthesis of related compounds.



I

The study was divided into two general areas. The first involves the replacement of the *p*-$NO_2$ group by other groups, chiefly by *p*-$SO_2CH_3$, to increase the solubility without changing the electronegativity, molecular volume, or ability of the molecule to participate in *p*-quinoid-type systems. In addition, the replacement by other groups such as H, *o*-$SO_2CH_3$, *p*-$SCH_3$, *p*-$SOCH_3$, *p*-$SO_2NH_2$, *p*-$NHCOCH_3$, *p*-$CH_3$, *p*-$OCH_3$, and 2′,5′-$OCH_3$ was included in this area to study the influence of the substituents on the pharmacological activity.

The second object was the study of the chemistry of the imidazo[1,2-*a*]pyridine ring; only 3-nitrosation[3] and 3-bromination[3] are known. We tried some of the characteristic reactions of the indole ring and succeeded in preparing Mannich bases, bromo, nitroso and amino, formyl, cyanomethyl, carboxymethyl, and carbamidomethyl derivatives in the 3-position of the ring.

Substituted 2-arylimidazo[1,2-*a*]pyridines (Table I, **1–13**) were readily prepared by condensation of 2-aminopyridine and 2-aminopicolines with ω-bromoacetophenones.[4] Methods of synthesis of imidazo[1,2-*a*]-pyridines described recently[5,6] by others have not been used in this study.

The *o*-methylsulfonylacetophenone, intermediate for the synthesis of compound **8**, was synthetized from 3-bromothiochromanone by hydrolysis to 2-mercaptoacetophenone that was methylated and oxidized with hydrogen peroxide in acetic acid.

The bromination of *p*-methylsulfoxyacetophenone with bromine in benzene led to *p*-methylmercapto-ω-dibromoacetophenone. The sulfoxy group was reduced by nascent HBr, another mole of bromine being formed. The equilibria represented by the following equations

$$R'R''SO + HX \rightleftharpoons (R'R''SOH)^+ X^-$$

$$(R'R''SOH)^+ X^- + HX \rightleftharpoons (R'R''SX)^+ X^- + H_2O$$

$$(R'R''SX)^+ X^- \rightleftharpoons R'R''S + X_2$$

probably explain the unexpected reaction[7]; indeed, by treating *p*-methylsulfoxyacetophenone with bromine in chloroform and sodium bicarbonate, *p*-methylsulfoxy-ω-bromoacetophenone was obtained in good yields. *p*-Sulfonamidoacetophenone was synthetized by oxidation with potassium permanganate of (*p*-sulfonamido)-ethylbenzene. Mannich bases (Table I, **22**, **24**, **25**, **29**, **30–33**, **35–38**, and **40–42**) were obtained in acetic acid, with stoichiometric quantities of secondary amines, formaldehyde, and 2-arylimidazo[1,2-*a*]pyridines. Treatment of the iodomethylate of the dimethylamino Mannich base of 2-(*p*-methylsulfonylphenyl)imidazo[1,2-*a*]-pyridine (Table I, **23**) with potassium cyanide in boiling water to obtain the cyanomethyl derivative as in the case of 3-dimethylaminomethylindole,[8] gave the carbamidomethyl derivative (Table I, **15**); the corresponding nitrile (**17**) was obtained from this compound with phosphorus oxychloride. 2-(*p*-Methylsulfonylphenyl)imidazo[1,2-*a*]pyridylacetic acid was prepared from the amide by saponifying it with sodium hydroxide in ethanol.

Nitroso derivatives (Table I, **19**, **26**, **34**, and **39**) were obtained by treating 2-arylimidazo[1,2-*a*]pyridines with sodium nitrite and mineral acids. Reduction of nitroso derivatives with zinc and acetic acid took place readily, giving amino derivatives (Table I, **20**, **27**, and **35**). Bromination of 2-(*p*-methylsulfonylphenyl)imidazo[1,2-*a*]pyridine was effected by bromine in acetic acid to give the 3-bromo derivative (Table I, **14**).

3-Dimethylamino derivatives (Table I, **21** and **28**) were obtained by Leuckart alkylation of the corresponding 3-amino compounds. The very promising pharmacological results of this series of compounds (see

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

(2) U. M. Teotino, L. Polo Friz, A. Gandini, and D. Della Bella, *Farmaco* (Pavia), *Ed. sci.*, **17**, 988 (1962).

(3) V. K. Matveev, *Bull. acad. sci. URSS, Classe sci. math. nat., Sér. chim.*, 1005 (1936); *Chem. Abstr.*, **31**, 53647 (1937).

(4) A. E. Tschitschibabin, *Ber.*, **58**, 1704 (1925).

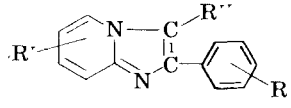
(5) J. Mandereau, P. Reynaud, and R. C. Moreau, *Compt. rend.*, **257**, 3434 (1963).

(6) A. M. Roe, *J. Chem. Soc.*, 2195 (1963).

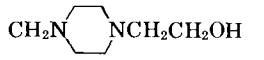
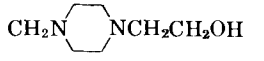
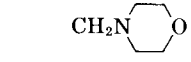
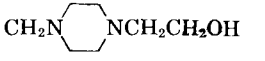
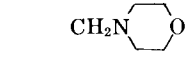
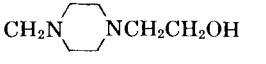
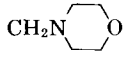
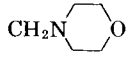
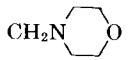
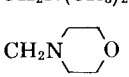
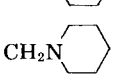
(7) E. Fromm, *Z. Angew. Chem.*, **24**, 1125 (1912).

(8) J. Thesing and F. Schülde, *Ber.*, **85**, 324 (1952).

TABLE I




| No. | R | R' | R'' | Derivative[a] | Recrystn. solvent | M.p., °C. | Formula | Mol. wt. | C, % Calcd. | C, % Found | H, % Calcd. | H, % Found | N, % Calcd. | N, % Found | O, % Calcd. | O, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[b] | H | H | H | A | 2-Propanol | 126–128 | $C_{13}H_{11}BrN_2$ | 275.1 | 56.55 | 56.49 | 4.38 | 4.31 | 10.15 | 9.98 | | |
| 2 | *p*-$CH_3$ | H | H | B | Water | 219–221 | $C_{14}H_{13}ClN_2 \cdot 0.5H_2O$ | 253.7 | 66.26 | 66.48 | 5.56 | 5.59 | 11.04 | 10.82 | | |
| 3[c] | *p*-$NO_2$ | H | H | C | Butanol | 254–255 | $C_{13}H_9N_3O_2$ | 239.2 | 65.26 | 65.01 | 3.79 | 3.88 | 17.57 | 17.36 | 13.38 | 13.15 |
| 4[c] | *p*-$NHCOCH_3$ | H | H | B | Methanol | 343–345 dec. | $C_{15}H_{14}ClN_3O$ | 287.7 | 62.61 | 62.49 | 4.90 | 5.08 | 14.61 | 14.61 | | |
| 5 | *p*-$OCH_3$ | H | H | B | Water | 241–244 dec. | $C_{14}H_{13}ClN_2O \cdot 0.5H_2O$ | 269.7 | 62.57 | 62.32 | 4.88 | 4.97 | 10.43 | 10.22 | 8.93 | 9.09 |
| 6 | 2,5-$OCH_3$ | H | H | A | Ethanol | 245–246 | $C_{15}H_{15}BrN_2O_2$ | 335.2 | 51.84 | 51.49 | 4.39 | 4.45 | 8.50 | 8.30 | 9.55 | 9.39 |
| 7 | *p*-$SO_2NH_2$ | H | H | C | Acetic acid–ethyl ether | 323–324 | $C_{13}H_{13}N_3O_2S$ | 273.3 | 57.13 | 56.75 | 4.06 | 4.13 | 15.37 | 15.29 | | |
| 8 | o-$SO_2CH_3$ | H | H | C | 2-Propanol | 177–178 | $C_{14}H_{12}N_2OS_2$ | 272.3 | 61.75 | 61.19 | 4.44 | 4.44 | 10.29 | 10.15 | 11.75 | 11.64 |
| 9 | *p*-$SCH_3$ | H | H | C | Ethanol | 162–163 | $C_{14}H_{12}N_2S$ | 240.3 | 69.97 | 69.60 | 5.03 | 5.01 | 11.66 | 11.62 | | |
| 10 | *p*-$SOCH_3$ | H | H | C | Benzene | 175–176 | $C_{14}H_{12}N_2OS$ | 256.3 | 65.60 | 66.05 | 4.72 | 4.88 | 10.93 | 11.29 | 6.25 | 6.18 |
| 11 | *p*-$SO_2CH_3$ | H | H | B | Water | 276–278 | $C_{14}H_{13}ClN_2O_2S \cdot H_2O$ | 326.8 | 51.45 | 51.81 | 4.63 | 4.48 | 8.57 | 8.36 | | |
| 12 | *p*-$SO_2CH_3$ | 5-$CH_3$ | H | B | Ethanol 10% aq. HCl | 280–282 dec. | $C_{15}H_{15}ClN_2O_2S$ | 322.8 | 55.81 | 55.70 | 4.68 | 4.58 | 8.68 | 8.75 | 9.91 | 9.75 |
| 13 | *p*-$SO_2CH_3$ | 7-$CH_3$ | H | C | Ethanol | 235–236 | $C_{15}H_{14}N_2O_2S$ | 286.3 | 62.92 | 62.77 | 4.93 | 4.97 | 9.79 | 9.76 | 11.18 | 11.31 |
| 14 | *p*-$SO_2CH_3$ | H | Br | C | Ethanol | 212–213 | $C_{14}H_{11}BrN_2O_2S$ | 351.2 | 47.87 | 47.86 | 3.16 | 3.02 | 7.98 | 7.83 | 9.11 | 9.22 |
| 15 | *p*-$SO_2CH_3$ | H | $CH_2CONH_2$ | C | Methanol | 271–272 | $C_{16}H_{15}N_3O_3S$ | 329.4 | 58.30 | 58.53 | 4.58 | 4.63 | 12.79 | 12.71 | | |
| 16 | *p*-$SO_2CH_3$ | H | $CH_2COOH$ | B | 10% aq. HCl | 318–319 dec. | $C_{16}H_{15}ClN_2O_4S$ | 366.8 | 52.39 | 52.36 | 4.12 | 4.04 | 7.64 | 7.80 | | |
| 17 | *p*-$SO_2CH_3$ | H | $CH_2CN$ | C | Methanol | 215–217 | $C_{16}H_{13}N_3O_2S$ | 311.3 | 61.72 | 61.48 | 4.21 | 4.33 | 13.49 | 13.37 | 10.28 | 10.32 |
| 18[d] | *p*-$SO_2CH_3$ | H | CHO | C | Methanol | 206–207 | $C_{15}H_{12}N_2O_3S$ | 300.3 | 59.98 | 60.42 | 4.03 | 4.08 | 9.33 | 9.20 | 15.98 | 15.91 |
| 19 | *p*-$SO_2CH_3$ | H | NO | C | Dioxane | 257–258 | $C_{14}H_{11}N_3O_3S$ | 301.3 | 55.80 | 55.86 | 3.68 | 3.75 | 13.95 | 13.76 | | |
| 20 | *p*-$SO_2CH_3$ | H | $NH_2$ | B | 10% aq. HCl | 334–336 dec. | $C_{15}H_{15}ClN_2O_2S$ | 323.8 | 51.93 | 51.98 | 4.36 | 4.30 | 12.97 | 12.97 | 9.88 | 10.07 |
| 21 | *p*-$SO_2CH_3$ | H | $N(CH_3)_2$ | B | 10% aq. HCl | 289–290 dec. | $C_{16}H_{18}ClN_3O_2S$ | 351.8 | 54.61 | 51.12 | 5.16 | 5.03 | 11.95 | 11.75 | | |
| 22 | *p*-$SO_2CH_3$ | H | $CH_2N(CH_3)_2$ | D | Methanol | 218–219 dec. | $C_{17}H_{21}Cl_2N_3O_2S \cdot H_2O$ | 420.3 | 48.57 | 48.81 | 5.52 | 5.63 | 10.00 | 10.12 | | |
| 23 | *p*-$SO_2CH_3$ | H | $CH_2N^+(CH_3)_3 \cdot I^-$ | ... | Ethanol | 207–208 | $C_{18}H_{22}IN_3O_2S$ | 471.5 | 45.86 | 45.79 | 4.71 | 4.65 | 8.91 | 8.86 | | |
| 24 | *p*-$SO_2CH_3$ | H |  | B | Ethanol | 204–206 dec. | $C_{18}H_{22}ClN_3O_3S$ | 406.5 | 56.05 | 55.94 | 5.45 | 5.38 | 10.32 | 10.27 | | |

| No. | R | R′ | R″ | Derivative[a] | Recrystn. solvent | M.p. °C. | Formula | Mol. wt. | C, % Calcd. | C, % Found | K, % Calcd. | K, % Found | N, % Calcd. | N, % Found | O, % Calcd. | O, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 25 | *p*-$SO_2CH_3$ | H |  | C | Ethanol | 71–73 dec. | $C_{21}H_{26}N_4O_3S$ | 414.5 | 60.85 | 60.67 | 6.32 | 6.24 | 13.52 | 13.79 | | |
| 26 | *o*-$SO_2CH_3$ | H | NO | C | Acetic acid | 206–208 dec. | $C_{14}H_{11}N_3O_3S$ | 301.3 | 55.80 | 55.73 | 3.68 | 3.58 | 13.95 | 13.90 | 15.93 | 15.69 |
| 27 | *o*-$SO_2CH_3$ | H | $NH_2$ | C | Ethanol | 189–190 | $C_{14}H_{13}N_3O_2S$ | 287.3 | 58.52 | 58.86 | 4.56 | 4.50 | 14.62 | 14.75 | | |
| 28 | *o*-$SO_2CH_3$ | H | $N(CH_3)_2$ | C | Ethanol | 173–174 | $C_{16}H_{17}N_3O_2S$ | 315.4 | 60.93 | 60.21 | 5.43 | 5.53 | 13.33 | 13.51 | | |
| 29 | *o*-$SO_2CH_3$ | H |  | C | Ethanol | 191–192 | $C_{21}H_{26}N_4O_3S$ | 314.5 | 60.85 | 60.62 | 6.32 | 6.36 | 13.52 | 13.70 | | |
| 30 | *p*-$SOCH_3$ | H |  | D | Ethanol | 193–194 dec. | $C_{19}H_{23}Cl_2N_3O_2S$ | 428.4 | 53.26 | 52.85 | 5.41 | 5.40 | 9.81 | 9.75 | 7.47 | 7.41 |
| 31 | *p*-$SOCH_3$ | H |  | E | 95% ethanol | 203–205 dec. | $C_{21}H_{26}Cl_3N_4O_2S$ | 504.9 | 49.95 | 49.70 | 5.19 | 5.01 | 11.10 | 10.91 | 6.34 | 6.21 |
| 32 | *p*-$SCH_3$ | H |  | C | Ethanol | 151–152 dec. | $C_{19}H_{21}N_3OS$ | 339.4 | 67.23 | 66.97 | 6.24 | 6.13 | 12.38 | 12.30 | | |
| 33 | *p*-$SCH_3$ | H |  | C | Ethanol | 84–86 dec. | $C_{21}H_{26}N_4OS$ | 382.5 | 65.94 | 65.69 | 6.85 | 6.70 | 14.65 | 14.61 | | |
| 34 | H | H | NO | C | Ethanol | 165–167 | $C_{13}H_{19}N_3O$ | 223.2 | 69.95 | 70.15 | 4.06 | 4.12 | 18.83 | 18.71 | 7.17 | 7.29 |
| 35 | H | H | $NH_2$ | C | Ethanol | 213–214 | $C_{13}H_{11}N_3$ | 209.2 | 74.62 | 74.99 | 5.30 | 5.50 | 20.08 | 19.84 | | |
| 36 | H | H |  | C | Benzene–petr. ether | 144–145 | $C_{18}H_{19}N_3O$ | 293.3 | 73.69 | 73.72 | 6.53 | 6.58 | 14.32 | 14.07 | 5.45 | 5.62 |
| 37 | *p*-$CH_3$ | H |  | C | *n*-Hexane | 127–128 | $C_{19}H_{21}N_3O$ | 307.4 | 74.24 | 74.15 | 6.88 | 6.89 | 13.67 | 13.62 | | |
| 38 | *p*-$OCH_3$ | H |  | C | Cyclohexane | 120–122 dec. | $C_{19}H_{21}N_3O_2$ | 323.4 | 70.56 | 71.08 | 6.55 | 6.71 | 13.00 | 12.82 | 9.89 | 9.70 |
| 39 | *p*-$NO_2$ | H | NO | C | Dioxane | 237–239 | $C_{13}H_{18}N_4O_3$ | 268.2 | 58.21 | 58.51 | 3.00 | 3.29 | 20.89 | 20.62 | 17.89 | 17.64 |
| 40 | *p*-$NO_2$ | H | $CH_2N(CH_3)_2$ | C | Ethanol | 142–144 | $C_{16}H_{16}N_4O_2$ | 296.3 | 64.85 | 64.77 | 5.44 | 5.58 | 18.91 | 18.82 | | |
| 41 | *p*-$NO_2$ | H |  | B | Ethanol–10% aq. HCl | 204–206 dec. | $C_{18}H_{19}ClN_4O_3$ | 374.8 | 57.68 | 57.59 | 5.11 | 5.03 | 14.95 | 14.73 | | |
| 42 | *p*-$NO_2$ | H |  | C | Methanol | 169–170 | $C_{19}H_{20}N_4O_2$ | 336.4 | 67.84 | 67.73 | 5.99 | 6.03 | 16.66 | 16.51 | 9.51 | 9.39 |

[a] A, hydrobromide; B, hydrochloride; C, base; D, dihydrochloride; E, trihydrochloride. [b] Free base has been reported previously by J. A. Kaye, C. L. Parris, and W. J. Burlant, *J. Am. Chem. Soc.*, **75,** 748 (1953). [c] The preparation of these compounds has been reported by T. Matsukawa and S. Ban, *J. Pharm. Soc. Japan*, **71,** 756 (1951); *Chem. Abstr.*, **46,** 8094*a* (1951). [d] Phenylhydrazone, m.p. 251°; N: calcd., 14.35; found, 14.28.

TABLE II

PHARMACOLOGICAL ACTIVITIES OF DERIVATIVES OF IMIDAZOLE

| | Analgesic activity | | | | | | Antiinflammatory activity | | | | Anticonvulsant activity | | | | | Acute toxicity[i] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Randall and Selitto[a] | | | | | | Rat-foot edema[c] | | | | | | | | | Fstd. | Gross |
| No. | Inflamed foot | Control foot | Hot-plate[b] | Electric stimulus[b] | Tail clip[c] | Phenyl-quinone[d] | Yeast | Carrageenan | Antipyretic activity Index[e] | Hypothermal activity Index[g] | Electroshock[h] convulsions | Pentylenetetrazol[h] Convulsions | Pentylenetetrazol[h] Death | Strychnine[i] Convulsions | Strychnine[i] Death | $LD_{50}$, mg./kg. mouse i.p. | Behavioral changes |
| 1 | 51 | 12 | 0 | 21 | 90 | 90 | 49 | 59 | 6.5 | 1.4 | 10 | 0 | 0 | 33 | 44 | 700 | *k–o* |
| 2 | 0 | 0 | 0 | 18 | 40 | 80 | 19 | 9 | 11.2 | 2.1 | 40 | 20 | 10 | 0 | 0 | 650 | *k, n* |
| 3 | 0 | 0 | 0 | 0 | 0 | 70 | 0 | 37 | 9.7 | 4.2 | 30 | 10 | 10 | 10 | 10 | 1500 | *k, l* |
| 4 | | | | | | | | | | | | | | | | 1000 | *k, n, p, q* |
| 5 | 22 | 0 | 0 | 42 | 40 | 90 | 36 | 57 | 4.3 | 1.0 | 100 | 100 | 50 | 11 | 11 | 700 | *k, n, p* |
| 6 | 0 | 0 | 53 | 0 | 0 | 50 | 15 | 0 | 8.2 | 3.4 | 0 | 0 | 0 | 0 | 0 | 500 | *n, p* |
| 7 | 0 | 0 | 21 | 26 | 0 | 0 | 0 | 21 | 1.9 | 0.8 | 0 | 0 | 0 | 0 | 0 | >3000 | *n, p* |
| 8 | 61 | 16 | 43 | 11 | 34 | 60 | 42 | 70 | 5.7 | 6.3 | 0 | 0 | 0 | 4 | 8 | 800 | *n, p, e* |
| 9 | 28 | 0 | 0 | 0 | 30 | 60 | 18 | 40 | 24.3 | 15.0 | 10 | 30 | 20 | 0 | 0 | 2500 | *k, s* |
| 10 | | | 33 | | | | | 42 | 15.7 | | | 60 | 80 | | | 600 | *m, p–r* |
| 11 | 143 | 22 | 57 | 49 | 30 | 85 | 68 | 59 | 28.4 | 11.0 | 48 | 36 | 12 | 72 | 84 | 800 | *k, m* |
| 12 | 67 | 37 | 124 | 0 | 30 | 60 | 48 | 29 | 27.5 | 21.0 | 100 | 60 | 50 | 16 | 4 | 1600 | *k, m, s* |
| 13 | 45 | 0 | 48 | 0 | 40 | 0 | 26 | 34 | 12.9 | 1.9 | 96 | 83 | 21 | 40 | 40 | >3000 | *k* |
| 14 | | | 28 | 0 | 30 | | | 36 | 7.2 | 1.8 | 10 | 20 | 20 | 0 | 0 | >3000 | *l, p, t* |
| 15 | | | 0 | 0 | 0 | 50 | | 0 | 7.6 | 4.0 | 0 | 0 | 0 | 0 | 0 | 2500 | *k* |
| 16 | 0 | 0 | 0 | 0 | 0 | 70 | 0 | 0 | 2.6 | −1.8 | 0 | 0 | 0 | 0 | 0 | >3000 | *l* |
| 17 | 19 | 0 | 23 | 0 | 25 | 40 | 30 | 22 | 4.7 | −1.9 | 0 | 0 | 0 | 0 | 0 | >3000 | *k* |
| 18 | 71 | 0 | 0 | 0 | 0 | 70 | 64 | 63 | 5.0 | −0.2 | 0 | 0 | 0 | 10 | 10 | >3000 | *l, p* |
| 19 | 0 | 0 | 65 | 53 | 0 | 40 | 0 | 23 | 11.8 | 0.0 | 0 | 0 | 50 | 0 | 0 | >3000 | *k* |
| 20 | 215 | 100 | 0 | 0 | 15 | 70 | 15 | 40 | 8.2 | 0.0 | 0 | 30 | 30 | 20 | 10 | 1600 | *m, p, r* |
| 21 | 23 | 0 | 54 | 58 | 55 | 50 | 28 | 34 | 1.5 | −2.1 | 40 | 0 | 0 | 0 | 0 | 400 | *n* |
| 22 | 130 | 66 | 20 | 7 | 40 | 40 | 51 | 63 | 10.7 | 11.0 | 8 | 16 | 16 | 12 | 24 | 400 | *s, t, e* |
| 23 | 0 | 0 | 0 | 0 | 0 | 70 | 0 | −72 | −0.1 | −1.1 | 0 | 0 | 0 | 0 | 0 | 650 | *k, l* |
| 24 | 68 | 0 | 24 | 2 | 36 | 61 | 26 | 33 | 10.5 | 2.4 | 16 | 32 | 24 | 4 | 8 | 350 | *k, m, s* |
| 25 | 0 | 0 | 0 | 30 | 0 | 0 | 22 | 26 | 2.8 | 1.6 | 0 | 40 | 40 | 0 | 0 | 500 | *k, w* |
| 26 | 10 | 0 | 23 | 13 | 25 | 70 | −23 | −17 | 6.6 | 2.2 | 0 | 10 | 0 | 10 | 0 | 2000 | *l, n, o* |
| 27 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 19 | 3.9 | 2.7 | 0 | 20 | 0 | 20 | 0 | 600 | *l, n, p* |
| 28 | 0 | 0 | 28 | 0 | 0 | 0 | 0 | 0 | 5.6 | 1.0 | 0 | 0 | 0 | 0 | 0 | 500 | *l, p* |
| 29 | 0 | 0 | 0 | 27 | 35 | 40 | 0 | 0 | 0.9 | 0.1 | 0 | 0 | 0 | 0 | 0 | 600 | *v, x* |
| 30 | 41 | 22 | 32 | 46 | 65 | 20 | 31 | 34 | −7.6 | −6.3 | 100 | 90 | 20 | 30 | 0 | 800 | *l, n, o, t* |
| 31 | 0 | 0 | 30 | 42 | 25 | 0 | 0 | 0 | 7.8 | −1.6 | 0 | 70 | 0 | 30 | 0 | 800 | *o–q* |
| 32 | 66 | 20 | 0 | 24 | 20 | 40 | 30 | 28 | 14.7 | 12.0 | 64 | 10 | 10 | 12 | 8 | >3000 | *k, o* |
| 33 | 0 | 0 | 29 | 23 | 30 | 66 | 0 | −38 | 5.9 | 0.1 | 0 | 20 | 30 | 0 | 0 | 500 | *l, q, e* |
| 34 | −18 | 0 | 44 | 26 | 70 | 70 | 12 | 49 | 11.1 | 1.0 | 0 | 0 | 0 | 0 | 0 | 700 | *k, q* |
| 35 | 0 | 0 | 42 | 26 | 70 | 70 | 22 | 35 | 14.6 | 4.6 | 0 | 20 | 20 | 0 | 0 | 650 | *k, q* |
| 36 | 0 | 0 | 18 | 0 | 0 | 0 | 28 | 24 | 3.2 | 0.7 | 0 | 0 | 0 | 0 | 0 | 150 | *q, v, w, y* |
| 37 | 77 | 17 | 23 | 40 | 70 | 40 | 44 | 28 | 5.0 | 5.9 | 48 | 70 | 10 | 12 | 0 | 400 | *k, s, v, z* |

| No. | Analgesic activity: Randell and Selitto[a] Inflamed foot | Randell and Selitto[a] Control foot | Hot-plate[b] | Electric stimulus[b] | Tail clip[c] | Phenylquinone | Antiinflammatory activity: Rat-foot edema[e] Yeast | Rat-foot edema[e] Carrageenan | Antipyretic activity Index[f] | Hypothermal activity Index[g] | Anticonvulsant activity: Electroshock[h] convulsions | Pentylenetetrazol[h] Convulsions | Pentylenetetrazol[h] Death | Strychnine[i] Convulsions | Strychnine[i] Death | Acute toxicity[j] Est. LD, mg./kg. mouse i.p. | Gross behavioral changes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 38 | | | 0 | | 0 | | | | | | | 20 | 0 | 0 | 0 | 400 | *k, n, q, s* |
| 39 | 0 | 0 | 33 | 38 | 30 | 90 | −9 | −14 | 6.9 | 1.0 | 0 | 0 | 0 | 0 | 0 | 700 | *v, y* |
| 40 | 20 | 14 | 26 | 23 | 40 | 30 | 13 | 45 | 4.0 | −1.6 | 0 | 0 | 0 | 0 | 0 | 200 | *s, v, x, z* |
| 41 | 0 | 0 | 33 | 0 | 0 | 0 | 33 | 39 | 13.3 | 4.1 | 40 | 90 | 0 | 0 | 0 | 650 | *s, v, x, z* |
| 42 | 21 | 0 | 0 | 32 | 50 | 50 | 0 | 59 | 4.0 | 0.7 | 0 | 0 | 10 | 0 | 0 | 800 | *k, s* |
| Acetylsalicylic acid | 20 | 0 | 0 | 0 | 18 | 65 | 33 | 62 | 5.9 | 2.8 | 14 | 0 | 0 | 0 | 0 | 420 | *l, n, r, s* |
| Aminopyrine | 108 | 25 | 89 | 0 | 53 | 100 | 65 | 62 | 8.6 | 2.8 | 52 | 40 | 20 | 4 | 4 | 308 | *v, w* |
| Phenylbutazone | 16 | 0 | 43 | 23 | 32 | 84 | 15 | 48 | 6.4 | 1.1 | 8 | 20 | 20 | 0 | 0 | 355 | *k, s* |
| Chlortenoxazine | 37 | 0 | 92 | −17 | 24 | 63 | 22 | 40 | 43.7 | 10.1 | 36 | 76 | 12 | 41 | 32 | 1190 | *k, m, p, u, n, q* |

[a] Per cent increase of pain threshold at 0.25 $LD_{50}$, rat *p.o.* [b] Per cent increase of pain threshold at 0.33 $LD_{50}$, mouse i.p. [c] Per cent of animals insensitive at 0.33 $LD_{50}$, mouse i.p. [d] Per cent of animals insensitive at 0.50 $LD_{50}$, mouse *p.o.* [e] Per cent edema inhibition at 0.25 $LD_{50}$, rat *p.o.* [f] Amount of reduction of fever in °C., compared with controls, caused by 0.25 $LD_{50}$, rat *p.o.* in a 6-hr. period after treatment (6 determinations). [g] Amount of reduction in temperature in °C., compared with controls, caused by 0.25 $LD_{50}$, rat *p.o.* in a 6-hr. period after treatment (6 determinations). [h] Per cent protection at 0.33 $LD_{50}$, mouse i.p. [i] Per cent protection at 0.50 $LD_{50}$, mouse i.p. [j] Approximate $LD_{50}$/168 hr. were determined by i.p. administration to groups of 5 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] Hypnosis. [n] ↓ muscle tone. [o] Salivation. [p] Depression. [q] Respiratory irregularity. [r] Hypothermia. [s] Clonic convulsions. [t] Writhing. [u] Narcosis. [v] Stimulation. [w] Ionic convulsions. [x] Tremors. [y] ↑ muscle tone. [z] Hypothermia.

Table II) has led us to complete our program of study in this field. Other imidazole derivatives such as 2-alkylimidazo[1,2-*a*]pyridine, imidazopyrimidines, imidazothiazoles, and imidazotriazines have been synthetized and screened.

We have also prepared compounds of the general formula which are closely related to indomethacin.[9] We




shall deal with the synthesis of these compounds and their pharmacological properties in forthcoming papers.

## Pharmacological Studies

In the absence of any laboratory test which may be considered directly related to clinical musculoskeletal conditions and due to the great variations in effectiveness of even therapeutically useful nonsteroidal antirheumatic agents in different experimental test models, it is through the use of a variety of biological systems, designed to disclose weak analgesic, antiinflammatory, antipyretic, and muscle-relaxant activity, that clinically acceptable new antiinflammatory drugs may be detected and evaluated in the laboratory. By using in each test drugs with known clinical activity as reference standard, new compounds that show comparable spectra of activity may be considered of some potential value also in man. In this way, the pharmacological properties of the test compounds were investigated in several basic screening procedures and their spectra of activity compared to those of the standards which included acetylsalicylic acid, aminopyrine, phenylbutazone, and chlortenoxazine.

**Methods.**—Adult NMRI mice of either sex weighing between 20–25 g. and male Sprague–Dawley rats weighing about 100–120 g. were used throughout these experiments. All compounds were administered as suspension in 2% aqueous starch solution at the doses and by the route specified in Table II. As parenteral administration has been shown to be misleading for antiinflammatory drugs, all compounds in these tests were administered by the oral route. The highest dose employed of a compound having low toxicity was 500 mg./kg. All tests were carried out at constant room temperature of 23° in air-conditioned laboratories.

**Acute Toxicity.**—Median lethal doses ($LD_{50}$), calculated by the method of Litchfield and Wilcoxon,[10] were derived from screening procedures using only 5 animals/dose and can only be considered as estimates. Concurrent with the toxicity range studies in mice and rats, careful gross observations of the animals were made at several dosage levels.

**Analgesic Activity.**—This action was studied 60 min. after oral administration of the drug in male rats in terms of alterations in mechanical pressure on the normal and the inflamed foot required to just elicit squeaking and/or flight reaction (struggle). A modification of the method of Randall and Selitto[11] was used. The degree of analgesia was calculated as the mean per cent increase in pain threshold of 10 treated rats over the average threshold of 10 control rats.

Eddy's method[12] measuring the reaction time of mice dropped on a hot plate (54.6–54.8°) was used to assess the thermal pain threshold 90, 60, and 30 min., and immediately before intraperitoneal drug administration and 30, 60, 90, and 120 min. after treatment. The difference between the average reaction time of the four pre-injection readings and that of the four post-injection readings was expressed as a percentage. The degree of analgesia was calculated as the mean per cent increase in thermal pain threshold of 30 treated mice over the average variation of pain threshold of 30 controls.

According to a modification of Luckner's method,[13] an electric

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

(10) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).

(11) L. O. Randall and J. J. Selitto, *Arch. Intern. Pharmacodyn*, **111**, 409 (1957).

(12) N. B. Eddy, C. F. Touchberry, and J. E. Lieberman, *J. Pharmacol. Exptl. Therap.*, **98**, 121 (1950).

(13) H. Luckner and R. Magun, *Z. Ges. Exptl. Med.*, **117**, 133 (1951).

stimulus was applied to the mouse tail and the squeak of the animal was taken as response. Parameters of the stimulus were as follows: amplitude 60 v., frequency 2/sec., pulse duration 4 msec. Each mouse was examined immediately before and 60 min. after i.p. administration and the difference in reaction time, expressed in per cent, served as criterion for analgesic effectiveness. The degree of analgesia was calculated as the mean per cent increase in reaction time of 20 treated mice over the average variation in reaction time of 20 controls.

Analgesia was also evaluated by the tail-clip technique of Bianchi, *et al.*[14] An artery clip was applied to the root of the tail for 30 sec. and the continuous attempt of the animal to remove the clip by biting was taken as response to the pain stimulus. The results were expressed as a percentage of previously sensitive mice showing insensitivity to the stimulus 30 min. after i.p. drugging. Twenty mice were used for each group.

Drug abolition of the typical syndrome produced in mice by intraperitoneal phenylquinone[15] was also used to evaluate analgesic effectiveness. Only mice that exhibited the syndrome repeatedly within 10 min. following injection of 0.25 ml. of a 0.02% water–alcohol solution of phenylquinone were used. The results were expressed as the percentage of mice not showing the syndrome between the 30th and 35th min. after oral administration. Twenty-five female mice were used for each group.

**Antiinflammatory Activity.**—The local antiinflammatory effect was studied by means of the rat-foot edema test,[16,17] employing carrageenan (λ-fraction)[18] and brewer's yeast as phlogistics. The test compounds were given orally immediately before injection into the plantar surface of the hind foot of 0.05 ml. of carrageenan solution (2%) or 0.1 ml. of yeast suspension (10%), and the volume of the foot was determined immediately and again 1, 2, 3, 4, and 5 hr. later. The difference between the first reading and the mean value of the 5 following determinations was recorded as "volume of edema." Foot volume was measured by Lenče's method.[19] The degree of antiinflammatory potency was calculated as the mean per cent inhibition of edema formation in 10 drug-treated rats against edema formation in 10 controls.

**Antipyretic and Hypothermal Activity.**—To evaluate the effect of the compounds on body temperature, their ability to lower rectal temperature in yeast-fevered (0.5 ml. of 15% yeast in 10% aqueous acacia mucilage/100 g. of body weight, injected into the muscle of both thighs, 17 hr. before drugging) and in nonfevered rats, was tested. The mean value of two temperature readings 60 min. and immediately before drugging was taken as base. The compounds were administered by stomach tube and temperatures were taken at 60-min. intervals for 6 hr. The total of the differences between each of the 6 readings thus obtained and the mean initial temperature constituted the temperature index.

**Anticonvulsant Activity.**—The anticonvulsant properties of the compounds were determined by methods patterned after those of Berger.[20] Tests were run 1 hr. after intraperitoneal administration of the drugs under test to groups of 30 mice (15 ♂ and 15 ♀).

Tonic extensor seizures were produced by electroshock applied through corneal electrodes. Supramaximal effect was obtained at 100 v., using a pulse rate of 150/sec. with a pulse width of 0.5 msec. for 0.3 sec. Abolition of the tonic extensor phase of the seizures was used as criterion for protection. The anticonvulsant potency of a compound was expressed as the percentage of mice protected from seizures. Pentamethylenetetrazol antagonism was determined in animals challenged with a certainly lethal dose of the convulsant (110–130 mg./kg. s.c.). Strychnine antagonism, used as criterion for the muscle-relaxant activity,[21] was determined in mice challenged with a dose of strychnine sulfate (1.9–2.1 mg./kg. s.c.) which in controls taken from the same batch as the animals to be treated proved to be lethal to 95–97% of mice within 10 min. of administration. Figures for protection afforded by a compound against either convulsant are based upon the percentage of mice protected from convulsions and upon mortality assessed 24 hr. after challenge.

## Results

Pharmacological results are reported in Table II, which also records the effects of the standard drugs included for comparison. A large number of the compounds prepared in this study exhibited significant pharmacological properties in different biological test systems. The general pattern of pharmacological activity encountered in these compounds was seen mainly in their effects on pain perception, local inflammation, and body temperature. However, there was a small, well-defined sedative, muscle-relaxant, and tranquilizing activity range associated with many of these compounds. Considerable variations of these effects were seen with each structural change, varying from agents that had no activity to those with a high potency, and significant changes in potency resulted even from minor changes in chemical structure as shown in Table I.

At doses approaching toxicity most of the compounds produced a depression of spontaneous motor activity as observed in intact mice and rats during toxicity tests. Some of the compounds displayed stimulating effects but even here the effects were only slight to moderate and, in many cases, were converted to depression when the doses were raised. Compounds **25** and **36** provoked typical tonic extensor seizures.

It is an important feature of these compounds that none showed significant activity on the mean blood pressure of urethan-anesthetized rats and that all the members of this series were found to be devoid of any significant inhibitory effect on monoamine oxidase.

**Analgesic Activity.**—Many of the compounds in this series exhibited activity in some or all of the experimental models used. Of particular interest are the results obtained in the Randall and Selitto procedure which utilizes selective inhibition of inflammatory pain as a criterion for antiinflammatory drugs.[22] When the structure of the more active compounds is compared to that of the simple unsubstituted 2-phenylimidazo-[1,2-*a*]pyridine (**1**), it would appear that replacement in R with a methyl (**37**), methylthio (**32**), or methylsulfonyl group (**8**, **11**, **12**, **18**, **20**, **22**, and **24**) enhanced analgesic activity. With the exception of compounds **32** and **37** (R″ = morpholinomethyl), **20** (R″ = amino), and **22** (R″ = dimethylaminomethyl), introduction of further substituents either in R′ or R″ in an already active molecule usually reduced (*e.g.*, **11** *vs.* **12** and **13**) or eliminated activity (*e.g.*, **11** *vs.* **16** and **19**).

Although there was only a little correlation with the activity found in the other tests, it seems worth noting that some of the most active compounds in the Randall and Selitto assay were also active in the hot-plate (**8**, **11**, and **12**), electric stimulation (**11** and **37**), tail-clip (**22** and **37**), or phenylquinone test (**8**, **11**, **12**, **18**, **20**, and **24**), or in all. The most interesting compounds were the methylsulfonyl analogs **11**, **20**, and **22**, which exhibited spectra of activity similar or superior to those shown by the reference drugs.

**Antiinflammatory Activity.**—A number of the agents caused marked reduction of the carrageenan- and yeast-induced edema of the rat foot. However, with excep-

(14) C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954).
(15) E. Siegmond, R. Cadmus, and G. Lu, *Proc. Soc. Exptl. Biol. Med.*, **95**, 729 (1957).
(16) R. Domenjoz, *Ann. Univ. Saraviensis*, **1**, 317 (1953).
(17) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exptl. Biol. N. Y.*, **111**, 544 (1962).
(18) The authors are indebted to Mr. M. H. Mafin from Marine Colloids, Inc., Springfield, N. J., for ample supplies of carrageenan λ-fraction.
(19) P. Lenče, *Arch. Intern. Pharmacodyn.*, **136**, 237 (1962).
(20) F. M. Berger, *J. Pharmacol. Exptl. Therap.*, **112**, 413 (1954).
(21) B. W. Horrom and T. E. Lynes, *J. Med. Chem.*, **6**, 528 (1963).
(22) B. Silvestrini, International Symposium on Nonsteroidal Anti-Inflammatory Drugs, Milan, Sept. 8–10, 1960.

tion of compound **5** (R = $OCH_3$), in these tests also only analogs with a methylsulfonyl group in R (**8**, **11**, **12**, **18**, and **22**) showed activity equal or superior to that exhibited by the simple unsubstituted 2-phenylimidazo[1,2-*a*]pyridine (**1**). It is worth noting that the position of the substituents in R had no significant effect on activity (**8** *vs.* **11**). Compounds **11** and **22**, in addition to being the most potent agents of this series against rat-foot inflammation, were also found to be among the most active analgesics when assayed in the Randall and Selitto test.

**Antipyretic and Hypothermal Activity.**—A number of compounds in this series lowered body temperature in the yeast-fevered and, to some extent also, in the normal rat. The unsubstituted compound **1** displayed only moderate activity in these tests and, with exception of compound **35** (R″ = amino), monosubstitution in R with a methylthio (**9**), methylsulfoxy (**10**), or a methylsulfonyl group (**11**) seems to be necessary for high activity. Further substitutions either in R′ or R″ in an already active compound, except in one case (**11** *vs.* **12**), seems to have a negative influence on the antipyretic and hypothermal activity (*e.g.*, **11** *vs.* **13**–**15**; **10** *vs.* **30** and **31**; and **9** *vs.* **32** and **33**). There appears to be a greater structure specificity for a high order of activity here than in any other test. The most critical substituents seems to be the methylsulfonyl and the methylthio group in R. However, alterations in the position of the methylsulfonyl group in R produced profound changes in activity as shown by a comparison of **11**, substituted *para*, and **8**, substituted *ortho*.

**Anticonvulsant Activity.**—Tonic extensor seizures produced by supramaximal electroshock were abolished by compounds **5**, **12**, **13**, and **30**. Convulsions elicited by pentamethylenetetrazole were antagonized by **5**, **10**, **12**, **13**, and **30**, and protection against lethal effects of this convulsant seemed to be more or less correlated with protection from its convulsions. Four compounds, **1**, **11**, **13**, and **22**, were found to give protection against toxicity of strychnine. When the anticonvulsant action of these 2-phenylimidazo[1,2-*a*]pyridine derivatives is analyzed, it is apparent that structural requirements for anticonvulsant activity against the three test systems are not related. The unsubstituted 2-phenylimidazo[1,2-*a*]pyridine (**1**) was found to be active against strychnine, but inactive in the other two tests, while introduction of a methylsulfonyl group in R not only produced more consistent activity against strychnine but also resulted in moderate antagonism against electroshock and pentamethylenetetrazol (**11**). Introduction of a 5- or 7-methyl group in the pyridine moiety of the active compound **11** produced profound activity against electroshock and pentamethylenetetrazole, but greatly reduced strychnine antagonism (*e.g.*, **11** *vs.* **12** and **13**). Substitutions in **11** at R″, in the other hand, gave either completely inactive (*e.g.*, **11** *vs.* **15**–**18**) or only slightly active compounds (*e.g.*, **11** *vs.* **14**, **19**, and **20**).

**General Comments.**—2-(*p*-Nitrophenyl)imidazo[1,2-*a*]pyridine (**3**) has been reported to possess antiinflammatory activity.[2] The purpose of the present study was to examine whether molecular modification might result in detection of new potential antirheumatic drugs. Forty-two 2-phenylimidazo[1,2-*a*]pyridine derivatives were prepared and assayed in a variety of pharmacological tests for analgesic, antiinflammatory, antipyretic, and muscle-relaxant (anticonvulsant) activity. The data reported in Tables I and II show that effects of variations in chemical structure on activity were rather unpredictable. Seldom did a particular structural modification lead to uniform alterations in activity in all tests. However, some points of interest did emerge and a few generalizations can be made. Thus, it may be stated that, although the simple unsubstituted 2-phenylimidazo[1,2-*a*]pyridine (**1**) has proved to have a spectrum of activity superior to that shown by the *p*-nitrophenyl derivative (**3**), introduction of other substituents led to a number of compounds with interesting activities in some or all of the tests. The substituent which appeared to be most important for high order of activity in the greatest number of tests was the methylsulfonyl group. Introduction of this group into the aryl moiety of the unsubstituted compound **1** produced compounds with potent analgesic, antiinflammatory, antipyretic and, in a few cases, muscle-relaxant properties. Further substitutions in R′ or R″ in an already active compound sometimes enhanced potency in single tests, but regarding spectrum of activity, these disubstitutions did not bring about any significant improvement.

Comparison of the spectrum of activity of the 2-phenylimidazo[1,2-*a*]pyridines with the corresponding data of reference standard drugs (which are included in Table II) indicated that some of the new derivatives reported here showed favorable properties as potential therapeutic agents. The most interesting substance for the purpose of therapeutic application appeared to be the 2-(*p*-methylsulfonylphenyl)imidazo[1,2-*a*]pyridine hydrochloride (**11**). In its pharmacological properties this compound seems to be related to aminopyrine with which it shared high analgesic activity in the classical Randall and Selitto assay and potent antiinflammatory activity in the carrageenan-induced edema of the rat paw, but by its high antipyretic activity and especially its protection of mice from strychnine toxicity, it also appeared to be related to chlortenoxazine. Obviously, the comparative evaluation of the active compounds will require further studies. The complete pharmacology of these compounds will be reported elsewhere.

## Experimental[23]

***p*-Methylmercaptoacetophenone.**[24]—To a cooled solution of 124.2 g. of methylthiophenol (1 mole) in 750 ml. of *sym*-tetrachlorethane were added 146 g. of anhydrous aluminum chloride (1.1 moles) and, dropwise, in 5 hr., 102 g. of acetic anhydride (1 mole), at −5°. The mixture was stirred 2 hr. at 25° and 5 hr. at 70° and poured into iced water acidified with 200 ml. of 37% HCl. The organic layer was separated and extracted with water, 10% $NaHCO_3$, and water. The solvent was removed *in vacuo* and the residue was distilled, giving 158 g. of product (95%), b.p. 135° (1 mm.), m.p. 83–84°.

***p*-Methylsulfoxy-ω-bromoacetophenone.**—To a solution of 182 g. of *p*-methylsulfoxyacetophenone (1 mole) in 900 ml. of chloroform was added 85 g. of $NaHCO_3$ (1 mole), and the mixture was heated at 60°. In 2 hr., with stirring, a solution of 160 g. of bromine (1 mole) in 100 ml. of chloroform, was added. After refluxing for 2 hr., the mixture was cooled, the solid was filtered, and the solvent was removed *in vacuo*. The residue was tritu-

(23) All melting points were taken in a Büchi melting point apparatus and are corrected.

(24) R. A. Cutler, R. J. Stenger, and C. M. Suter, *J. Am. Chem. Soc.*, **74**, 5475 (1952), reported m.p. 80–82° (uncor.).

rated with hexane and filtered. Crystallization from 400 ml. of benzene yielded 215 g. (82%) of product, m.p. 99–101°.

*Anal.* Calcd. for $C_9H_9BrO_3S$: C, 41.40; H, 3.46; Br, 30.62. Found: C, 41.05; H, 3.14; Br, 30.31.

**p-Methylmercapto-ω-dibromoacetophenone.**—A solution of 18.2 g. of *p*-methylsulfoxyacetophenone (0.1 mole) in 50 ml. of benzene was heated at 70°. In 2 hr., with stirring, 16 g. of bromine (0.1 mole) was added. After cooling, the solvent was removed *in vacuo*. The residue was crystallized from cyclohexane, and 29 g. of a product, m.p. 107–108°, was obtained. This product was identified by analysis and mixture melting point with the product obtained by bromination of *p*-methylmercaptoacetophenone with 2 moles of bromine.

*Anal.* Calcd. for $C_9H_8Br_2OS$: C, 33.36; H, 2.49; Br, 49.33; O, 4.93; S, 9.89. Found: C, 33.48; H, 2.50; Br, 49.58; O, 4.87; S, 9.77.

**o-Methylmercaptoacetophenone.**—A solution of 243 g. of 3-bromothiochromanone (1 mole) in 1300 ml. of boiling ethanol was added to 1700 ml. of 2 *N* NaOH (3.4 moles). After refluxing for 0.5 hr., the ethanol was removed *in vacuo*. To the filtered, cooled, and stirred aqueous solution was added 138 g. of methyl sulfate (1.1 moles). After 2 hr. a crystalline product was filtered and dissolved in ethyl ether; the solvent was washed with water, dried, and removed *in vacuo*. Distillation of the residue afforded 77 g. (47%) of a colorless liquid, b.p. 123° (1.5 mm.). Triturated with hexane, the product solidified, m.p. 47–49°.

*Anal.* Calcd. for $C_9H_{10}OS$: C, 65.01; H, 6.06; O, 9.63; S, 19.29. Found: C, 64.97; H, 6.05; O, 9.78; S, 19.07.

**o-Methylsulfonylacetophenone.**—To a solution of 166 g. of *o*-methylmercaptoacetophenone (1 mole) in 150 ml. of glacial acetic acid, at 65°, was added a solution of 186 ml. of 41% $H_2O_2$ (2.2 moles) in 60 ml. of glacial acetic acid. After stirring for 3 hr., the solution was poured into 1700 ml. of water. After cooling, a crystalline solid separated. Recrystallization from ethanol, yielded 165 g. (83%), m.p. 103–105°.

*Anal.* Calcd. for $C_9H_{10}O_3S$: C, 54.53; H, 5.09; O, 24.21; S, 16.17. Found: C, 54.75; H, 5.09; O, 24.02; S, 15.97.

**2-(p-Methylsulfonylphenyl)imidazo[1,2-a]pyridine Hydrochloride (Table I, 11).**—To a solution of 188.2 g. of freshly distilled 2-aminopyridine (2 moles) in 1000 ml. of ethanol, was added 277.1 g. of *p*-methylsulfonylphenyl-ω-bromoacetophenone (1 mole). The mixture was heated at 60° and stirred for 3 hr. The crystalline solid was filtered and washed with warm ethanol. Crystallization from HCl yielded 242 g. of product (75%), m.p. 276–278°. The free base had m.p. 242–244°. By the same method, starting from 2-aminopyridine and 2-aminopicolines and adding substituted ω-bromoacetophenones, compounds **1–10** (Table I) were prepared.

**2-(p-Methylsulfonylphenyl)-3-dimethylaminomethylimidazo[1,2-a]pyridine Dihydrochloride (Table I, 22).**—A solution of 272 g. of 2-(*p*-methylsulfonylphenyl)imidazo[1,2-*a*]pyridine (1 mole) in 2000 ml. of glacial acetic acid was mixed with a solution of 50 g. of dimethylamine (1.1 moles) and 82.5 ml. of 40% formalin (1.1 moles) in 450 ml. of glacial acetic acid. After warming at 60° for 3 hr., the mixture was cooled and poured into ice-water, made alkaline with 20% NaOH, and extracted with methylene chloride; the solvent was dried and removed *in vacuo*. The residue was taken up in warm ethanol and treated with dry HCl. The precipitated dihydrochloride was recrystallized from ethanol to give 340 g. (81%).

By the same method the Mannich bases **24, 25, 29–33, 36–38,** and **40–42** (Table I) were prepared.

**2-(p-Methylsulfonylphenyl)-3-carbamidomethylimidazo[1,2-a]pyridine (Table I, 15).**—To a solution of 19.4 g. of NaCN (0.4 mole) in 180 ml. of water was added 47.1 g. of 2-(*p*-methylsulfonylphenyl)-3-dimethylaminomethylimidazo[1,2-*a*]pyridine iodomethylate (Table I, **23**) (0.1 mole). After refluxing for 3 hr. the solution was cooled and filtered. Crystallization from methanol yielded 27.5 g. (86%) of product.

**2-(p-Methylsulfonylphenyl)-3-cyanomethylimidazo[1,2-a]pyridine (Table I, 17).**—A suspension of 32.9 g. of 2-(*p*-methylsulfonylphenyl)-3-carbamidomethylimidazo[1,2-*a*]pyridine (0.1 mole) was heated at 120° with 125 ml. of phosphorus oxychloride. The excess phosphorus oxychloride was removed *in vacuo*, and the residue was taken up in 500 ml. of iced water, made alkaline with $Na_2CO_3$, and filtered. Crystallization from dimethylformamide–water afforded 24.4 g. of product (78%), m.p. 215–217°.

**2-(p-Methylsulfonylphenyl)-3-carboxymethylimidazo[1,2-a]pyridine (Table I, 16).**—A solution of 32.9 g. of 2-(*p*-methylsulfonylphenyl)-3-carbamidomethylimidazo[1,2-*a*]pyridine (0.1 mole) and 80 g. of KOH (1.43 moles) in 80 ml. of water and 320 ml. of ethanol was refluxed 18 hr. After cooling, the solution was acidified with 37% HCl and the precipitate was filtered. By crystallization from 37% HCl, 25.6 g. of product (70%) was obtained, m.p. 318–319° dec.

**2-(p-Methylsulfonylphenyl)-3-nitrosoimidazo[1,2-a]pyridine (Table I, 19).**—In 450 ml. of warm water, 32.6 g. of 2-(*p*-methylsulfonylphenyl)imidazo[1,2-*a*]pyridine hydrochloride (0.1 mole) was dissolved. At 45° 10 ml. of 37% HCl and, in 1 hr., a solution of 8.28 g. of sodium nitrite (0.1 mole) in 100 ml. of water were added. After cooling, 600 ml. of water was added. The solution was made alkaline with $Na_2CO_3$ and filtered. The yield of product was 28.9 g. (96%), m.p. 257–258°. By the same method were prepared compounds **26, 34,** and **39** (Table I).

**2-(p-Methylsulfonylphenyl)-3-aminoimidazo[1,2-a]pyridine Hydrochloride (Table I, 20).**—To a suspension of 30.1 g. of 2-(*p*-methylsulfonylphenyl)-3-nitrosoimidazo[1,2-*a*]pyridine (0.1 mole) in 200 ml. of water and 140 ml. of acetic acid 27 g. of powdered zinc was added over a period of 2 hr. After stirring for 2 hr., the solution was heated at 80° for 1 hr., filtered, and made alkaline with diluted NaOH. The free base was dissolved in warm 37% HCl and, after chilling, the precipitated hydrochloride was filtered. The yield was 26.3 g. (80.5%), m.p. 334–336°. With the same method were prepared compounds **27** and **35** (Table I).

**2-(p-Methylsulfonylphenyl)-3-bromoimidazo[1,2-a]pyridine (Table I, 14).**—To a solution of 27.2 g. of 2-(*p*-methylsulfonylphenyl)imidazo[1,2-*a*]pyridine in 100 ml. of glacial acetic acid at 65°, 16 g. of bromine was added. A white crystalline solid precipitated. It was filtered and washed with cold water, and the suspension was made alkaline with $Na_2CO_3$, yielding 31.5 g. (90%) of product, m.p. 212–213°.

**2-(p-Methylsulfonylphenyl)-3-dimethylaminoimidazo[1,2-a]pyridine Hydrochloride (Table I, 21).**—A solution of 28.7 g. of 2-(*p*-methylsulfonylphenyl)-3-aminoimidazo[1,2-*a*]pyridine (0.1 mole) in 10 ml. of formic acid was heated at 100° for 2 hr. After cooling, water was added and the solid obtained was filtered and recrystallized from absolute ethanol. 2-(*p*-Methylsulfonylphenyl)-3-formylaminoimidazo[1,2-*a*]pyridine (18 g., 57%) was obtained, m.p. 272–273°.

*Anal.* Calcd. for $C_{15}H_{13}N_3O_3S$: C, 57.13; H, 4.16; N, 13.33. Found: C, 56.97; H, 4.30; N, 13.51.

A solution of 15.75 g. of this compound in 12 ml. of formic acid and 9 ml. of 40% formalin was heated at 120° for 24 hr. After cooling, the solution was acidified with 5 ml. of 37% HCl and evaporated *in vacuo*. The residue was crystallized from diluted HCl with the aid of Norit. The yield was 7.8 g. (44.75%), m.p. 289–291°.

**2-(o-Methylsulfonylphenyl)-3-dimethylaminoimidazo[1,2-a]pyridine (Table I, 28).**—A solution of 28.7 g. of 2-(*o*-methylsulfonylphenyl)-3-aminoimidazo[1,2-*a*]pyridine (0.1 mole) in 36 ml. of formic acid and 16 ml. of 40% formalin was heated at 120° for 12 hr. After cooling, the solution was acidified with 30 ml. of 37% HCl and evaporated *in vacuo*. The residue was triturated with water and was made alkaline with NaOH. The solid obtained was crystallized from absolute ethanol giving 14 g. of product, m.p. 174–175°.