References and Notes

(1) This work was presented in part at the 174th National Meeting of the American Chemical Society, Chicago, Ill., Aug 29–Sept 1, 1977, CARB 20.
(2) J. J. Baker, A. M. Mian, and J. R. Tittensor, *Tetrahedron*, **30**, 2939 (1974), and references cited therein.
(3) W. H. Prusoff and D. C. Ward, *Biochem. Pharmacol.*, **25**, 1233 (1976).
(4) A. Bloch in "Drug Design", Vol. IV, E. J. Ariens, Ed., Academic Press, New York and London, 1973, pp 285–378.
(5) R. N. Prasad, A. Fung, K. Tietje, H. H. Stein, and H. D. Brondyk, *J. Med. Chem.*, **19**, 1180 (1976), and references cited therein.
(6) J. F. Henderson and M. L. Battell, *Biochem. Pharmacol.*, **25**, 1915 (1976).
(7) O. Kraupp, German Patent 2610985 (1977); *Chem. Abstr.*, **88**, 7312d (1978).
(8) K. C. Tsou, N. J. Santora, and E. E. Miller, *J. Med. Chem.*, **12**, 173 (1969).
(9) J. J. Baker, P. Mellish, C. Riddle, A. R. Somerville, and J. R. Tittenson, *J. Med. Chem.*, **17**, 764 (1974).
(10) P. Langen and G. Kowollik, *Eur. J. Biochem.*, **6**, 344 (1968).
(11) J. P. Neenan and W. Rohde, *J. Med. Chem.*, **16**, 580 (1973).
(12) R. W. Binkley, *J. Org. Chem.*, **42**, 1216 (1977), and references cited therein.
(13) G. P. Moss, C. B. Reese, K. Schofield, R. Shapiro, and Lord A. Todd, *J. Chem. Soc.*, 1149 (1963).
(14) A. S. Jones, A. R. Williamson, and M. Winkley, *Carbohydr. Res.*, 1, 187 (1965), and references cited therein.
(15) P. Howgate, A. S. Jones, and J. R. Tittensor, *J. Chem. Soc. C*, 276 (1968).
(16) J. Zemlicka, R. Gasser, J. V. Freisler, and J. P. Horwitz, *J. Am. Chem. Soc.*, **94**, 3213 (1972); *J. Org. Chem.*, **38**, 990 (1973).
(17) A. A. Akhrem, A. G. Lapko, I. A. Mikhailopulo, and V. A. Timoshehuk, *Carbohydr. Res.*, **54**, C1–C2 (1977).
(18) M. Sela and H. Ungar-Waron in "Methods in Enzymology", L. Grossman and K. Moldave, Ed., Academic Press, New York, N.Y., 1968, pp 900–902.
(19) H. Pischel, A. Holy, and G. Wagner, *Collect. Czech. Chem. Commun.*, **39**, 3773 (1974).
(20) C. B. Reese, K. Schofield, K. Shapiro, and A. R. Todd, *Proc. Chem. Soc., London*, 290 (1960).
(21) K. Heyns and H. Paulsen in "Newer Methods in Preparative Organic Chemistry", Vol. II, W. Foerst, Ed., Academic Press, New York, N.Y., 1963, pp 303–335.
(22) K. Imai and M. Honjo, *Chem. Pharm. Bull.*, **13**, 7 (1965).
(23) J. Zemlicka and J. P. Horwitz, *J. Am. Chem. Soc.*, **97**, 4089 (1975).
(24) H. Follmann and H. Witzel, *Eur. J. Biochem.*, **77**, 451 (1977).
(25) E. Darzynkiewicz, M. Remin, A. Dworak, and D. Shugar, *Cancer Biochem. Biophys.*, 1, 85 (1975).
(26) B. Sunners, L. H. Piette, and W. G. Schneider, *Can. J. Chem.*, **38**, 681 (1960).
(27) B. R. Baker in "Design of Active-Site-Directed Irreversible Enzyme Inhibitors", B. R. Baker, Ed., Wiley, New York, N.Y., 1967, p 75.
(28) Abbreviations: FUra, 5-fluorouracil; BrUra, 5-bromouracil; IUra, 5-iodouracil; dUrd, 2′-deoxyuridine; FdUrd, 5-fluoro-2′-deoxyuridine; BrdUrd, 5-bromo-2′-deoxyuridine; IdUrd, 5-iodo-2′-deoxyuridine; IdCyd, 5-iodo-2′-deoxycytidine; BrdCyd, 5-bromo-2′-deoxycytidine.
(29) Y. C. Cheng and W. H. Prusoff, *Biochemistry*, **13**, 1179 (1974).
(30) Y. C. Cheng and W. H. Prusoff, *Biochemistry*, **12**, 2162 (1973).
(31) B. R. Baker, T. J. Schwan, and D. V. Santi, *J. Med. Chem.*, **9**, 66 (1966).
(32) W. H. Prusoff, M. S. Chen, T. S. Lin, G. T. Shiau, and R. F. Schinazi, unpublished results.
(33) D. Roberts, *Biochemistry*, **5**, 3546 (1966).
(34) We thank Dr. K. Scanlon of this department and Dr. T. Kalman of SUNY at Buffalo for these data.
(35) P. K. Chang and A. D. Welch, *Biochem. Parmacol.*, **8**, 327; **6**, 50 (1961).
(36) T. S. Lin and W. H. Prusoff, *J. Med. Chem.*, **21**, 106 (1978).
(37) M. Hashmi in "Assays of Vitamins in Pharmaceutical Preparations", Wiley, London and New York, 1973, p 225.
(38) Y. C. Cheng and M. Ostrander, *J. Biol. Chem.*, **251**, 2605 (1976).
(39) M. S. Chen and W. H. Prusoff, *Biochemistry*, **16**, 3310 (1977).

Phosphorus–Nitrogen Compounds. 22. Synthesis and Antitumor Activity of Arylsulfonylhydrazone Analogues

L. A. Cates,* D. J. Good, G. S. Jones, and T. L. Lemke

Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Houston, Houston, Texas 77004.
Received April 14, 1978

A series of pyridine-2-carboxaldehyde *N*-oxide and pyridine-2-carboxaldehyde (thio)phosphoric hydrazones and two cupric chelates was synthesized. The hydrazones, chelates, and combinations of hydrazones and cupric chloride were tested against mice bearing P388 lymphocytic leukemia, Sarcoma 180, or Ehrlich carcinoma ascites cells. The effects of various structural modifications of the hydrazones on antineoplastic activity for this latter system were determined. In general, the pyridine-2-carboxaldehyde thiophosphoric monohydrazones containing *P*-phenyl or *P*-phenoxy substituents possessed the highest activity when concurrently administered with cupric ion, whereas the ligands themselves were inactive. Two of the compounds were prepared with *P*-hydroxyl groups to permit increased hydrophilicity. The ability of the hydrazones to chelate cupric, ferrous, and cobaltous salts was investigated, and discrepancies between determined and calculated log *P* values for three compounds are discussed.

A series of arylsulfonylhydrazones of aromatic aldehydes has been investigated for murine antineoplastic properties, with the establishment of relationships between such activity and structure.[1,2] In general, the greatest effects resulted when the aldehyde portion was 2-formylpyridine *N*-oxide and when bulky substituents were on the sulfur atom. In the case of the related 5-hydroxy-2-formylpyridine thiosemicarbazones, relatively large groupings on the N^4 are also beneficial with regard to the effect against the Sarcoma 180 animal model system but not as concerns inhibition of ribonucleoside diphosphate reductase.[3] Thiophosphoric hydrazones related to the highly investigated oncolytic 2-formylpyridine thiosemicarbazones have been prepared and tested against Ehrlich carcinoma, with significant activity noted with certain cupric chelates and with concurrently administered ligands and cupric chloride.[4]

The present paper describes the synthesis and biological evaluation against three murine tumor systems of phosphoric and thiophosphoric hydrazones of 2-formylpyridine

0022-2623/78/1821-1146$01.00/0

Table I. Antitumor Effects of Phosphoric Hydrazones 1-12, Concurrently Administered Ligand-Metal Salts 1-Cu to 12-Cu, and Cupric Complexes 13 and 14

compd	dose, mg/kg[b]	% T/C[a] Ehrlich[c]	Sarcoma 180[c]	P388[d]
1	100	190	81	108
2	100	160		108
3	100	144	93	113
4	100	123	89	103
5	100	118	107	
6	100	115	95	103
7	100	114	93	87
8	100	108	96	111
9	100	104	79	114
10	100			117
11	100			111
12	100			102
13	6.1	160	99	89
14	6.1			92
	12.2			133
1-Cu	50-8	150	87	95
2-Cu	40-8	98		78
3-Cu[e]	40-8	204	106	94
4-Cu[f]	40-8	166	85	89
5-Cu[f]	40-8	164	87	
6-Cu	40-8	163	79	99
7-Cu[g]	40-8	269	141	97
8-Cu	40-8	135	126	73
9-Cu	50-8	204	106	87
10-Cu	40-8			92
11-Cu	50-8			95
12-Cu	40-8			94
$CuCl_2$ control	8	98	98	94
cell control		16.3 ± 0.6[h]	18.2 ± 0.3[h]	10.3 ± 0.2[h]

[a] Average survival time (treated/control) × 100. Mice that survived more than 50 days were calculated as 50-day survivors in the calculation of average survival time. [b] Doses for combinations 1-Cu to 12-Cu are for ligand-cupric chloride. [c] Dose was administered once daily to groups of six mice for six consecutive days, beginning 24 h after tumor transplantation. [d] Dose was administered once daily to groups of six mice for nine consecutive days, beginning 24 h after tumor transplantation. [e] Two 50-day survivors. [f] One 50-day survivor. [g] Three 50-day survivors. [h] Average survival time, days ± SE.

and 2-formylpyridine *N*-oxide, with the ascertaining of structure–activity relationships for this class of anticancer agents for Ehrlich carcinoma. In addition, the chelating properties of the new agents, as well as the log *P* values (logarithm of the partition constant of a compound in octanol–water) of three members, were investigated.

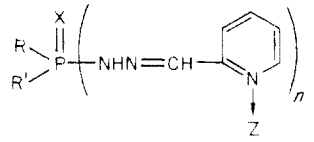
Results and Discussion

The antitumor activity of the phosphorus hydrazone ligands, cupric chelates and concurrently administered ligands, and cupric chloride was determined by measuring their effects against Ehrlich carcinoma, Sarcoma 180, and P388 lymphocytic leukemia; the results are shown in Table I. The ligands were, for the most part, designed as pairs which differ by only a single structural feature to permit the ascertaining of the effect of this modification on antineoplastic activity. The following comparisons were made: S vs. O (thiophosphorus vs. phosphorus derivatives), oxides vs. nonoxides (2-formylpyridine *N*-oxides vs. 2-formylpyridines), monohydrazones vs. dihydrazones, and *P*-phenoxy vs. *P*-ethoxy vs. *P*-phenyl compounds. Against Ehrlich carcinoma, it was noted that S > O (**2** vs. **8**), nonoxide > oxide (**1** vs. **9**), and, perhaps, monohydrazone > dihydrazone (**3** vs. **4**). This comparison proves partially valid when examining the three most active compounds, **1**–**3**, two of which are monohydrazones or thiophosphorus derivatives with the nonoxide having the highest activity. A similar investigation of ligand–cupric combinations also showed that S > O (**2**–Cu vs. **8**–Cu) and monohydrazone > dihydrazone (**3**–Cu vs. **4**–Cu), but, under these conditions, again the effect of oxide vs. nonoxide is not clear since opposing results are found (**9**–Cu vs. **1**–Cu and **7**–Cu vs. **4**–Cu). With either ligand alone or in combination with cupric chloride, bulky substituents on the phosphoryl group were favorable in the case of the most active agents, **1** and **7**–Cu. This relationship pertains when examining the analogous ligands **3** (two phenoxys) and **8** (two ethoxys). Since only two ligand–cupric combinations, **7**–Cu and **8**–Cu, displayed activity in the more intractable Sarcoma 180 system, no correlation of structure with activity is possible, but, again, it was shown that with the combination **7**–Cu containing a phenyl substituent possessed the highest activity. None of the ligands or ligand–metal combinations displayed activity against P388 lymphocytic leukemia, but one of the two cupric chelates tested, **14**, was active at 12.2 mg/kg. This corresponds to the relatively greater effect over ligand alone, previously noted with cupric chelates which are alkoxy analogues of **14**.[4]

Since the chelating ability of 2-formyl heterocyclic thiosemicarbazones[5] and their phosphorus analogues[4] is important to oncolytic activity, the complexing properties of ligands **2**–**7** and **9**–**12** were also investigated. All thiophosphoric hydrazones chelated cupric ion, but only three phosphoric hydrazones, **5**, **6**, and **10**, in which the pyridine nitrogen atom is in the free (nonoxide) form, had this ability. Thus, **10** complexes Cu^{II} while its *N*-oxide does not; **2** also lacked this property. In this type of hydrazone it appears, therefore, that converting the pyridine moieties to their *N*-oxides, which do not possess nitrogen electron pairs, renders this portion of the molecule incapable of participating in chelation. Although **5** and **6** chelate Cu^{II} and Co^{II}, it is likely that the acidic hydroxyl groups present in these agents contribute to complexing ability. This is substantiated by the finding that all complexing compounds chelated Cu^{II} in a ligand–metal ratio of 2:1 with the exception of **6**, which has both hydroxyl and pyridyl groups free and showed greater complexing ability (1:1). Lack of ability to chelate Fe^{II} and Co^{II} was noted with **2**–**4**, **8**, and **9**, while both **5** and **6** complexed this latter ion. Chelation appears to play an important role in the oncolytic properties of these agents, since ligand–cupric combinations provide an average % T/C increase of 41.8 in the Ehrlich system over ligands alone. The only nonchelator, **2**, although active per se, was the sole compound of those tested not active against Ehrlich carcinoma when administered concurrently with cupric chloride.

The use of phosphorus in lieu of carbon, in the case of thiosemicarbazones, or of sulfur, in the arylsulfonylhydrazones, was intended to provide for two possibly advantageous structural features. Pentavalent phosphorus permits the synthesis of dihydrazones with supposedly greater chelating ability while still allowing attachment of a bulky substituent on this atom. Also, phosphorus can have affixed this latter, required group as well as a water-solubilizing moiety. A problem with various thiosemicarbazones is the lack of sufficient water solubility, and attempts have been made to overcome this difficulty with the introduction of hydroxyl and amino moieties on their heterocyclic portions. In general, this approach was not successful due to more rapid metabolism and elimi-

Table II. Physical Constants of Phosphoric Hydrazones and Chelates



compd	R	R′	*n*	X	Z	mp, °C	formula	analyses
1[a]	phenyl		2	S				
2	ethoxy	ethoxy	1	O	O	63-66	$C_{10}H_{16}N_3O_4P$	C, H, N
3[b]	phenoxy	phenoxy	1	S	O	158-160	$C_{18}H_{16}N_3O_3PS$	C, H, N
4[b]	phenoxy		2	S	O	224-225 dec	$C_{18}H_{17}N_6O_3PS$	C, H, N
5[b]	phenoxy	hydroxy	1	O	O	175-178 dec	$C_{12}H_{12}N_3O_4P\cdot0.5H_2O$	C, H, N
6	phenoxy	hydroxy	1	O		143-146 dec	$C_{12}H_{12}N_3O_3P\cdot0.5H_2O$	C, H, N
7[b]	phenoxy		2	S		169-171	$C_{18}H_{17}N_6OPS$	C, H, N
8[a]	ethoxy	ethoxy	1	S	O			
9	phenyl		2	S	O	208 dec	$C_{18}H_{17}N_6O_2PS$	C, H, N
10[c]	phenoxy	phenoxy	1	O		135-136	$C_{18}H_{16}N_3O_3P$	C, H, N
11[c]	phenoxy	phenoxy	1	O	O	134-135	$C_{18}H_{16}N_3O_4P$	C, H, N
12[c]	phenoxy	phenoxy	1	S		132-135	$C_{18}H_{16}N_3O_2PS$	C, H, N
13[d]	phenoxy	phenoxy	1	O		205-207	$C_{18}H_{16}N_3O_3P\cdot CuCl_2$	C, H, N; Cu,[e] Cl[f]
14[d]	phenoxy	phenoxy	1	S		175-177 dec	$C_{18}H_{16}N_3O_2PS\cdot CuCl_2\cdot2.5H_2O$	C, H, Cu; N,[g] Cl[h]

[a] The properties were the same as those previously reported.[4] [b] From EtOH. [c] From C_6H_6-petroleum ether (bp 40-60 °C). [d] Cupric chelates. [e] Cu: calcd, 13.03; found, 14.23. [f] Cl: calcd, 14.54; found, 12.85. [g] N: calcd, 7.65; found, 9.40. [h] Cl: calcd, 12.92; found, 13.70.

nation.[5] Monoacids **5** and **6** were, therefore, designed to provide for greater hydrophilicity on the side chain. An examination of the bioactivity of compounds tested indicates that no benefit is derived from either dihydrazone formation or increased hydrophilicity on the side chain.

Inasmuch as the hydrophilic–lipophilic character of bioactive compounds constitutes an important factor in absorption, transport, and distribution, this property of three compounds was examined. While introduction of a hydroxyl group on the phosphorus atom increases hydrophilicity, another modification, conversion of the pyridine moiety to the *N*-oxide, should have an even greater effect. Pyridine *N*-oxide has a log *P* value (octanol–water) of −1.69, compared to +0.65 for pyridine.[6] Comparing the experimentally determined log *P* values for **7** and **4** of +1.62 (calculated, +1.67[7]) and +1.28 (calculated, −3.01[8]), respectively, it is obvious that the *N*-oxygen confers considerably less water solubility than would be expected. This difference is also noted when comparing the calculated log *P* of **5** of −2.27[9] with its determined value of −0.68. These discrepancies can be accounted for on the basis of intramolecular hydrogen bonding occurring between the *N*-oxygen and N^3-hydrogen, which would reduce the extent of similar bonding with polar solvent molecules.

In view of the suggestion that phosphoramides possess higher log *P* values, compared to carboxamides, due to intramolecular hydrogen bonding,[10] the nearly identical calculated and determined log *P* values for **4** are unexpected. Again, in this case, such bonding may play a role in this apparent discrepancy, whereby competition between pyridine nitrogen pair electrons and phosphoryl oxygen electrons for the N^3-hydrogen permits greater availability by the latter for intermolecular bonding with solvent molecules.

Several other discrepancies between calculated and determined log *P* values, with regard to phosphoramides, are found in the literature. An example is the determined log *P* value (octanol–water) for cyclophosphamide of +0.63,[6] compared to its values of +2.52 and +2.87 calculated from hexamethylphosphoric triamide[11] and tripropyl phosphate,[12] respectively. The unusual solubility characteristics of some types of organophosphorus compounds have been observed for many years. It appears that, as yet, there are no established partition coefficient constants for such agents that can be used as an aid in drug design.

Experimental Section

Melting points were taken in a Thomas–Hoover capillary melting point apparatus and are uncorrected. NMR spectra were obtained with a Varian EM360 spectrometer using Me_4Si as an internal standard, and IR absorptions were determined with a Perkin–Elmer 283 spectrophotometer with KBr pellets. Both NMR and IR spectra were consistent with the assigned structure. Visible and UV spectral determinations were made on a Beckman DB-GT spectrophotometer. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, Ga., or Galbraith Laboratories, Inc., Knoxville, Tenn. Where analyses are indicated only by symbols of the elements, the analytical results for those elements were within ±0.4% of theoretical values unless otherwise stated. As previously reported,[4,13,14] determined elemental analyses of copper chelates often do not agree with theoretical values.

Antitumor Activity. The ascites cell forms of Ehrlich carcinoma, grown in female Swiss albino mice, and of Sarcoma 180 and P388 lymphocytic leukemia, grown in DBA_2 female mice, were employed. Transplantation of 4×10^6 (Ehrlich carcinoma or Sarcoma 180) or 10^5 (P388 lymphocytic leukemia) cells, in 0.1-mL suspensions administered intraperitoneally, was carried out using donor mice bearing 7-day tumor growths. Experimental details concerning the preparation of the cell suspension, preparation of single agents and concurrently administered ligand–cupric chloride solutions, and suspensions and the volumes of these that were administered have been described earlier.[4] Compounds **1**–**12** were arbitrarily administered at a previously determined, nontoxic dose of 100 mg/kg, while other determinations, also using female Swiss albino mice, required reduction of **13**, **14**, and **1**-Cu to **12**-Cu to maximum nontoxic doses. Treatment of mice bearing ascites cells with 8 mg/kg of cupric chloride did not significantly extend survival time or produce host toxicity, as was the case in a previous study.[4]

Chelation Studies. EtOH solutions of **2**–**7** and **9**–**12** and cupric chloride dihydrate, cobaltous chloride hexahydrate, and ferrous chloride tetrahydrate were added such that the metal ion concentration remained constant at 1.67×10^{-5} M, while the ligand concentration was increased in increments from 1.67 to 8.35×10^{-5} M. These solutions produced, when chelation occurred, a hyperchromic shift in the 300–400-nm region as the ligand concentration was increased. The chelation ratios were calculated from the concentration of ligand and metal ion at which no greater absorbance was observed.

Partition Studies. The log *P* values (octanol–water, buffered to pH 7.4) of **4**, **5**, and **7** were ascertained using the procedure described by Purcell et al.[15] Determinations, with a standard

deviation of 0.04, were made at two different concentrations and volumes of phases. Following shaking for 30 min, the layers were separated, the aqueous portion was centrifuged at 9900g and then filtered, and absorbances were measured at 301, 261, and 290 nm for **4**, **5**, and **7**, respectively. In addition, the log P value of **5** was determined to be −0.76 using an octanol–water system, with the concentration of **5** determined as the inorganic phosphate by treating the sample with a sulfuric acid–perchloric acid solution[16] and quantitating phosphate concentrations using the method of Berenblum and Chain.[17]

Syntheses. The hydrazones (starting hydrazides' references cited) **2**,[18] **4–7**, **10**, and **11**,[19] **9**,[4] and **3** and **12**[20] (Table II) were prepared by refluxing the appropriate hydrazide with pyridine-2-carboxaldehyde or pyridine-2-carboxaldehyde 1-oxide[21] in absolute EtOH for 1 h in the presence of HOAc (1 mL). Where no recrystallization solvent is indicated, the products were isolated from the reaction mixture, washed with water, and dried in vacuo. No acetic acid was used in the case of **2**, **4**, **7**, or **9**. Diphenyl phosphorochloridothionate, required for the preparation of the hydrazide leading to **3** and **12**, was synthesized according to the procedure of Autenrieth and Hildebrand.[22] The MnO_2 required for the synthesis of pyridine-2-carboxaldehyde 1-oxide is best prepared by the method of Sondheimer et al.[23] Cupric chelates **13** and **14** were prepared by adding a saturated solution of cupric chloride dihydrate, in absolute EtOH, dropwise to **10** (1.5 g) or **12** (1.0 g) in 20 mL of absolute EtOH until no additional precipitate formed. The reaction mixtures were stirred 15 min. The precipitates were collected, washed several times with triply distilled H_2O, and dried in vacuo.

Acknowledgment. This investigation was supported by U.S. Public Health Service Grant CA-19882-01. The authors wish to thank Norman Caron of the Department of Biophysical Sciences, University of Houston, for conducting the Sarcoma 180 and P388 murine tests.

References and Notes

(1) A. C. Sartorelli, K. C. Agrawal, B. A. Booth, J. Pittman, D. Bartholomew, and A. D. Broom, *J. Med. Chem.*, **19**, 830 (1976).
(2) K. C. Agrawal and A. C. Sartorelli, *J. Med. Chem.*, **21**, 218 (1978).
(3) K. C. Agrawal, M. H. Lee, B. A. Booth, E. C. Moore, and A. C. Sartorelli, *J. Med. Chem.*, **17**, 934 (1974).
(4) L. A. Cates, Y. M. Cho, L. K. Smith, L. Williams, and T. L. Lemke, *J. Med. Chem.*, **19**, 1133 (1976).
(5) K. C. Agrawal, B. A. Booth, S. M. DeNuzzo, and A. C. Sartorelli, *J. Med. Chem.*, **19**, 1209 (1976), and references cited therein.
(6) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 525 (1971).
(7) 2[methylamine (−0.57) + double bond (−0.30) + pyridine (+0.65)] + diethyl phenylphosphorothioate (+3.46) − 2Et (+1.00 each) + intramolecular hydrogen bonding (+0.65), given N and O are equivalent.
(8) 7 − 2(pyridine) (+0.65) + 2(pyridine *N*-oxide) (−1.69).
(9) Methylamine (−0.57) + double bond (−0.30) + pyridine *N*-oxide (−1.69) + diethyl phenylphosphorate (+1.64) − 2Et (+1.00 each) + intramolecular hydrogen bonding (+0.65), given N and O are equivalent.
(10) L. A. Cates, M. B. Cramer, and L. Williams, *J. Med. Chem.*, **21**, 143 (1978).
(11) Hexamethylphosphoric triamide (+0.28) − 2(branching of functional group) (−0.20 each) + Me (+0.50) + 2Cl (+0.39 each) + ring closure (−0.09) + intramolecular hydrogen bonding (+0.65).
(12) Tripropylphosphine oxide (+2.53) − 2Me (+0.50 each) + 2Cl (+0.39 each) + ring closure (−0.09) + intramolecular hydrogen bonding (+0.65).
(13) B. A. Gingras, R. W. Hornal, and C. H. Bayley, *Can. J. Chem.*, **38**, 712 (1960).
(14) G. J. Van Giessen and H. G. Petering, *J. Med. Chem.*, **11**, 695 (1968).
(15) W. P. Purcell, G. E. Bass, and J. M. Clayton, "Strategy of Drug Design", Wiley, New York, N.Y., 1973, p 127.
(16) C. S. Hanes and F. A. Isherwood, *Nature (London)*, **164**, 1107 (1949).
(17) I. Berenblum and E. Chain, *Biochem. J.*, **32**, 295 (1938).
(18) M. Nagazawa and Y. Imamiya, Japanese Patent 11 013 (1962); *Chem. Abstr.*, **59**, 3833 (1963).
(19) R. Klement and K. O. Knollmuller, *Chem. Ber.*, **93**, 834 (1960).
(20) H. Tolkmith, *J. Am. Chem. Soc.*, **84**, 2097 (1962).
(21) E. P. Papadopoulos, A. Jarrar, and C. H. Issidorides, *J. Org. Chem.*, **31**, 615 (1966).
(22) W. Autenrieth and O. Hildebrand, *Ber. Dtsch. Chem. Ges.*, **31**, 1094 (1898).
(23) F. Sondheimer, O. Mancera, M. Urquiza, and G. Rosenkranz, *J. Am. Chem. Soc.*, **77**, 4145 (1955).

Synthesis of Spiro[isobenzofuran-1(3*H*),4'-piperidines] as Potential Central Nervous System Agents. 4. Central Nervous System Depressants

Richard C. Allen, Victor J. Bauer, Raymond W. Kosley, Jr., Arthur R. McFadden, Gregory M. Shutske,*

Chemical Research Department

Michael L. Cornfeldt, Stuart Fielding, Harry M. Geyer, III, and Jeffrey C. Wilker

Department of Pharmacology, Hoechst-Roussel Pharmaceuticals, Inc., Somerville, New Jersey 08876. *Received May 26, 1978*

The synthesis of 1'-[3-(4-fluorobenzoyl)propyl]-3-phenylspiro[isobenzofuran-1(3*H*),4'-piperidine] (**2a**) and eight halo and methoxy analogues is described. The compounds were generally more potent per os than chlorpromazine in the Sidman avoidance paradigm in rats and less potent than haloperidol. 1'-[3-(4-Fluorobenzoyl)propyl]-3-(4-fluorophenyl)spiro[isobenzofuran-1(3*H*),4'-piperidine] (**2e**) approached the per os potency of haloperidol in this test and was shown to be active in inhibiting monkey avoidance also. Compound **2e** was much less active than haloperidol in antagonizing apomorphine-induced emesis in dogs, apomorphine-induced stereotypy in rats, and amphetamine-induced circling in lesioned rats. This lack of nonselective, dopamine-receptor blocking effects makes **2e** attractive as a potential neuroleptic.

In the first three papers in this series[1] we described a number of 3-phenylspiro[isobenzofuran-1(3*H*),4'-piperidines] of general formula **1**. Compounds **1a** and **1b** exhibited potent antitetrabenazine activity and **1c** was active in lowering blood pressure in the spontaneously hypertensive rat. Since several compounds in the 3-aryl-

0022-2623/78/1821-1149$01.00/0