New Compounds

Some Semicarbazones and Thiosemicarbazones[1]

ABELARDO P. MARTINEZ AND WILLIAM W. LEE

Life Sciences Research, Stanford Research Institute, Menlo Park, California 94025

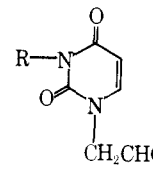
Received June 1, 1967

A number of semicarbazones and thiosemicarbazones of aromatic and heterocyclic aldehydes have been examined for antiviral and antitumor activities[2] since Brockman, *et al.*,[3] first observed the antileukemic effect of 2-formylpyridine thiosemicarbazone. In a search for other antitumor agents of this type, we have converted the aldehydes **1–5**, which were available from other studies, to the derivatives listed in Table I.

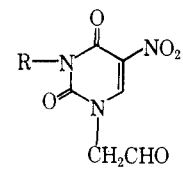
TABLE I
DERIVATIVES OF ALDEHYDES **1–5**

RCHO	Deriv.[a]	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % Other	Found, % C	Found, % H	Found, % Other
1	M	95	243.5–244.0	$C_8H_{11}N_5O_2S$	39.8	4.60	*S*, 13.3	39.7	4.56	*S*, 13.4
	S	100	225.0–225.5	$C_7H_9N_5O_3 \cdot 0.5H_2O$	38.2	4.58		38.2	4.83	
	T	78	223–228[b]	$C_7H_9N_5O_2S$	37.0	3.98		37.0	4.21	
2	S	67	229–230	$C_{10}H_{14}N_8O_4$	38.7	4.54		39.0	4.66	
	T	72	225–227	$C_{10}H_{14}N_8O_2S_2$	35.1	4.12		34.9	4.19	
3	M	60	215–216	$C_{12}H_{18}N_8O_2S_2$	38.9	4.99	*S*, 17.3	38.7	5.05	*S*, 17.1
	S	100	250.0–250.5	$C_{11}H_8N_6O_2$	52.8	3.15	*N*, 32.8	52.9	3.30	*N*, 32.8
	M	82	206–210	$C_8H_{10}N_6O_2S$	33.6	3.52	*N*, 29.4	33.3	3.76	*N*, 29.3
	T	86	238–240	$C_{11}H_8N_6O_4S$	30.9	2.95		31.0	3.10	
4	M	67	225–227[b]	$C_{12}H_{17}N_9O_4S_2$	34.7	4.13	*N*, 30.2	34.5	3.91	*N*, 29.9
	T	70	153–155	$C_{12}H_{16}ClFN_4S_2$	47.6	5.32	*N*, 18.5	47.8	5.74	*N*, 18.2
5	M	59	135–136	$C_{13}H_{18}ClFN_4S$	49.2	5.73	*N*, 17.7	48.8	6.03	*N*, 18.0

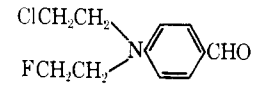
[a] The types of derivatives are: M, N⁴-methylthiosemicarbazone; *S*, semicarbazone; T, thiosemicarbazone. For **2** and **4**, the dialdehydes, these stand for the bis derivatives. [b] Recrystallized from aqueous *N*,*N*-dimethylformamide.



1, R = H
2, R = CH_2CHO



3, R = H
4, R = CH_2CHO



5

Experimental Section

The semicarbazone-type derivatives were prepared by the usual procedure.[4] The derivatives were all crystallized from or washed with ethanol or aqueous ethanol, except as noted.

Acknowledgments.—The authors are grateful to Dr. Leon Goodman for advice and encouragement, to Mr. O. P. Crews and staff for preparation of some starting materials, and to Dr. Peter Lim and staff for infrared spectra.

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. PH-43-64-500. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center.

(2) (a) J. M. Vendini, D. R. Sheldan, and A. Golden, *Cancer Res.* (Suppl), **24**, 149 (1964); (b) S. Watanabe and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **11**, 1551 (1963); (c) F. A. French and E. J. Blanz, Jr., *J. Med. Chem.*, **9**, 585 (1966); (d) M. A. Chirigos, F. J. Ranscker, L. A. Kamel, G. R. Fanning, and A. Goldin, *Cancer Res.*, **23**, 1646 (1963).

(3) R. W. Brockman, J. R. Thompson, M. J. Bell, and H. E. Skipper, *ibid.*, **16**, 167 (1956).

(4) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systemic Identification of Organic Compounds," 4th ed, John Wiley and Sons, Inc., New York, N. Y., 1962, p 218.

Trifluoromethylbenzaldoximes[1]

CHARLES F. BAREKNECHT[2a] AND TIM R. WESTBY[2b]

College of Pharmacy, Idaho State University, Pocatello, Idaho 83201

Received May 2, 1967

Oximes exhibit skeletal muscle relaxant activity.[3] Preliminary pharmacological screening has shown that *m*-trifluoromethylbenzaldoxime has this action.[4] This series of compounds (see Table I) was synthesized so that the relationship of the oxime configuration and the trifluoromethyl substituent position to the pharmacological potency could be evaluated.

Experimental Section

Trifluoromethylbenzaldehydes.—The corresponding trifluoromethylbenzonitriles[5] were converted to the aldehydes by reaction

(1) This work was supported by National Science Foundation Undergraduate Research Participation Grant GY-246.

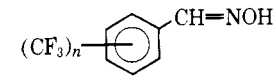
(2) (a) College of Pharmacy, University of Iowa, Iowa City, Iowa; (b) National Science Foundation Undergraduate Research Participant.

(3) (a) J. A. Skorez, J. T. Suh, C. I. Judd, M. Finkelstein, and A. C. Conway, *J. Med. Chem.*, **9**, 656 (1966); (b) E. R. Garrett, *J. Pharm. Sci.*, **51**, 410 (1962); (c) L. W. Blockus, G. M. Everett, and R. K. Richards, *Federation Proc.*, **17**, 350 (1958).

(4) Decreased locomotor activity and muscle tone of the trunk and limbs was observed in mice at 32 mg/kg iv with an MED_{50} of 18 mg/kg iv. The pharmacological screening was conducted by the Toxicity Screening Branch, U. S. Army Edgewood Arsenal, Md., to whom the authors are indebted.

TABLE I

TRIFLUOROMETHYLBENZALDOXIMES



No.	Config	Isomer	n	Yield, %	Mp, °C[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, %[b] C	Found, %[b] H	Found, %[b] N
1	*syn*	*ortho*	1	85	54–55	$C_8H_6F_3NO$	50.80	3.26	7.41	50.74	3.35	7.26
2	*syn*	*meta*	1	77	46–47	$C_8H_6F_3NO$	50.80	3.26	7.41	50.69	3.26	7.19
3	*syn*	*para*	1	70	100–101	$C_8H_6F_3NO$	50.80	3.26	7.41	51.07	3.25	7.51
4	*syn*	3,5-di	2	85	92–93	$C_9H_5F_6NO$	42.02	1.95	5.44	42.37	2.04	5.36
5	*anti*	3,5-di	2	1	134–135	$C_9H_5F_6NO$	42.02	1.95	5.44	42.19	2.28	5.35

[a] Melting points were determined on a Thomas–Hoover capillary apparatus and are corrected. [b] Analyses were performed by Galbraith Laboratories, Inc., Nashville, Tenn.

with Raney nickel and formic acid.[6] Yields of 58, 74, 75% were obtained for the *ortho*, *meta*, and *para* isomers, respectively. The aldehydes were used without further purification in the next reaction.

***syn*-Trifluoromethylbenzaldoximes.**—Vogel's[7] procedure was followed, but the pure *syn* configuration was obtained only with 1. Compounds **2** and **3** contained traces of the *anti* compounds, while **4** contained a larger amount of the *anti* configuration. The crystalline *syn* configurations, 1–**4**, were obtained by column chromatography on silica gel with benzene–ethyl acetate (10:1 as the eluting solvent.

***anti*-Trifluoromethylbenzaldoxime Hydrochlorides.**—Saturation of the ethereal solutions of the *syn*-oximes with anhydrous HCl gas and subsequent cooling caused precipitation of the salts which were collected on sintered-glass funnels.[7] The yields of the salts were essentially quantitative. No salt could be formed from **1**. The unusual behavior of the *ortho* isomer will be the subject of a later communication.

***anti*-Trifluoromethylbenzaldoximes.**—Decomposition of the *anti*-hydrochloride salts of **2** and **3** with 10% aqueous Na_2CO_3 followed by ether extraction resulted in a mixture of configurational isomers. Column chromatography of the mixtures failed to give crystalline *anti* isomers. Compound **5** was separated from **4** by silica gel column chromatography.

(5) Purchased from Pierce Chemical Co., Rockford, Ill.
(6) B. Staskum and O. G. Backeberg, *J. Chem. Soc.*, 5880 (1964).
(7) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, John Wiley and Sons, Inc., New York, N. Y., 1956, p 719.

Book Reviews

Anticancer Agents. By FRANCES E. KNOCK. A Monograph in American Lectures in Living Chemistry. Edited by I. NEWTON KUGELMANS. Charles C Thomas, Publisher, Springfield, Ill. 1966. ix + 272 pp. 25 × 18 cm. $15.50.

As they walked along a path one evening, a group of men came upon a friend searching the ground under a lamp post. The searcher explained that he was looking for a key, whereupon the strollers joined in the search. After examining the area for some minutes, they asked, "are you certain that the key is here?" The friend answered, "oh no, it is someplace along this path, but the light is here." Examination of this well-known story with respect to the friend's approach to his dilemma, discloses something about his judgment. He knew that the key was to be found someplace within rather broad limits. Since the light was within these limits, the decision to look under it was sound because the key would be more easily found if it were there. His decision to commit, by his silence before questioning, his friends to look in the same place was clearly unsound. The man fell into the "trap" of assessing his situation as presenting a choice between two alternatives which were not mutually exclusive. Dr. Knock seems to have fallen into a similar "trap" in her editorial comments on the status of cancer chemotherapeutic studies in the United States; but more about this later.

The book purports ". . . to present related aspects of surgical–chemical treatment of cancer, at preclinical and clinical levels." Further, the author pleads ". . . for patient-centered cancer therapy, . . . for coordinated surgical–chemical treatment of cancer individualized in accord with the chemical requirements of each patient's own cancer cells." The desirability of these objectives is unquestioned. The author's approach to selection of a drug on the basis of biological, chemical, and drug-sensitivity testing of the patient's tumor is interesting and worthy of note even though such techniques have not yet been fruitful in general. Otherwise, the book presents a concise review of factors known to influence the etiology, development, and treatment of experimental or clinical cancer, and will be informative for scientific investigators who are not directly involved in cancer therapy; for those who are in the field, it will seem to be somewhat superficial.

Factors known to influence the development of cancer in the laboratory animal or in humans including chemical, physical, and viral carcinogens are discussed briefly. The author has noted the value of early diagnosis. She has reviewed broadly the techniques of surgery and radiation and their value, and has properly pointed out their limitations in cases of disseminated disease. New and older approaches which have been exploited to varying extents are discussed. These range from the use of surgery plus chemotherapy to the use of immunotherapeutic techniques; the latter yet to be shown as beneficial. Reviewed with clarity are some of the known biochemical and pharmacological actions of some widely known anticancer agents as well as other agents that are of interest because of their similarity in action to known anticancer drugs. The student of biochemistry and pharmacology may find these discussions interesting inasmuch as many important biochemical pathways, and the ways in which they are inhibited, are covered. The main types of compounds considered are alkylating agents, sulfhydryl inhibitors, antimetabolites, plant and antibiotic filtrate products, steroids and hormones, and miscellaneous drugs including methylglyoxal bisguanylhydrazone, methylhydrazines, terephthalanilides, *o,p'*-DDD, hydroxyurea, quinacrines, urethan, and indomethacin. Scant mention is made of bischloroethylnitrosourea, and cytosine arabinoside is not mentioned. Both of the latter have been in clinical trial.

This leaves Dr. Knock's comments on the ethics involved in entering a new drug into clinical trial and her thoughts on the philosophy of searching for new chemotherapeutic agents. It is unfortunate that on this latter point, concerning the national program for uncovering new anticancer drugs, Dr. Knock has