Syntheses and Screening of Some Trifluoromethyl Pyrazoles

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Steroid pyrazoles[1] and pyrazoles substituted with simple groups,[2] especially CF_3,[3] are reported to possess various types of biological activity. An interest in the effects of the CF_3 substituent has prompted us to investigate the activity of pyrazole derivatives which may be regarded as molecular moieties of such prototypes (see Table I). These new compds result from the courtesy of Wyeth Laboratories, Radnor, Pa., in the following tests: antipentylenetetrazole,[5] antitremorine,[6] and antimorphine[7] activity, antagonism to reserpine ptosis,[8] activity on blood pressure in hypertensive rats,[9] antiinflammatory[10,11] and the following antibiotic tests: antibacterial *in vitro* (see Experimental Section), antiamebic *in vitro*, antitrichomonal *in vitro*, and antihelmintic activity;[12] antiviral effect against: influenza A/AA/57, B/MD, A2 Taiwan, and herpes simplex.[13,14]

With the exception of **1** which was about 0.3% as effective as an amebicide compared with emetine and **3** which had 0.5 to 1% the trichomonacidal activity of metronidazole, none of these compds showed activity in these tests.

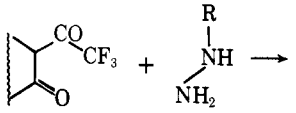
TABLE I

TRIFLUOROMETHYL PYRAZOLE DERIVATIVES

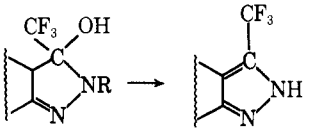
Compd	Mp, °C	% yield	Method	Formula	Analyses	Recryst from
1	134–137	70	B	$C_7H_7F_3N_2$	C, H, F, N	C_6H_{14}
2	128–129	81	B	$C_8H_9F_3N_2$	C, H, F, N	C_6H_{14}
3	109–110	89	B	$C_{10}H_{11}F_3N_2$	C, H, F, N	*a*
4	162–163	88	B	$C_9H_{11}F_3N_2$	C, H, F, N	C_6H_{14}
5	162–164	87	A	$C_8H_{10}F_3N_3OS$	C, H, F, N, S	EtOH
6	95–96	87.5	A	$C_9H_{12}F_3N_3OS$	C, H, F, N, S	C_6H_{14}
7a	135–136	68	A	$C_{11}H_{14}F_3N_3OS$	C, H, F, N, S	C_7H_{16}
7b	136–138	44	C	$C_{10}H_{13}F_3N_2O$	C, H, F, N	C_7H_{16}[b]
8	132–132.5	81	A	$C_{11}H_{16}F_3N_3OS$	C, H, F, N, S	C_7H_{16}
9	116.5–118	54	A	$C_{10}H_{14}F_3N_3OS$	C, H, F, N, S	PhMe
10	142–143	87	A	$C_6H_8F_3N_3OS$	C, H, F, N	Cyclohexane–EtOAc

[a] Triturated with boiling H_2O. [b] Followed by sublimation.

reaction of various α-trifluoroacetyl ketones with hydrazine (R = H) and thiosemicarbizide (R = $CSNH_2$) to give in some cases a 3,4-condensed-5-



R = H, $CSNH_2$



hydroxy-5-trifluoromethyl dihydropyrazole or in other cases, depending on reaction conditions, the 3,4-condensed-5-trifluoromethyl pyrazoles directly (see Chart I).

In the reaction of 2-trifluoroacetylcyclopentanone[4] and thiosemicarbazide, a stable enol (**5**) was obtained which did not cyclize. This perhaps is due to stabilization by H bonding to the C=S group. A recheck of **7b** after several months showed spontaneous loss of H_2O resulting in **3**.

Biological Tests.—Compds **1–9** were screened through the courtesy of Wyeth Laboratories, Radnor, Pa., in the following tests: antipentylenetetrazole,[5] antitremorine,[6] and antimorphine[7] activity, antagonism to reserpine ptosis,[8] activity on blood pressure in hypertensive rats,[9] antiinflammatory[10,11] and the following antibiotic tests: antibacterial *in vitro* (see Experimental Section), antiamebic *in vitro*, antitrichomonal *in vitro*, and antihelmintic activity;[12] antiviral effect against: influenza A/AA/57, B/MD, A2 Taiwan, and herpes simplex.[13,14]

With the exception of **1** which was about 0.3% as effective as an amebicide compared with emetine and **3** which had 0.5 to 1% the trichomonacidal activity of metronidazole, none of these compds showed activity in these tests.

Experimental Section

All melting points were taken on a Thomas-Hoover apparatus and are uncorr. The ir and nmr spectra were detd for all compds and are in accord with the structures. Elemental analyses were carried out by Galbraith Labs, Knoxville, Tenn. Anal. results for the indicated elements were all within 0.3% of the calcd values.

The α-trifluoroacetyl derivatives of cyclopentanone and cyclohexanone were prepd by described procedures[15] as was α-trifluoroacetylacetone.[4] The remaining α-trifluoroacetyl derivatives of 4,4-dimethylcyclohexanone and cycloheptanone were similarly prepd.[15] (see Table II) with the exception of 4,4-dimethyl-Δ^2-cyclohexenone in which NaH was substituted for NaOMe in the condensation.

5-Hydroxy-5-trifluoromethyldihydropyrazoles. Method A.—The trifluoroacetyl ketone (0.1 mole) in abs EtOH was mixed with an aq soln of thiosemicarbazide·HCl (0.1 mole) contg 10% excess HCl and was allowed to stand for 1 hr. The mixt was

(1) R. O. Clinton, A. J. Manson, F. W. Stoner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickenson, and C. Carabateas, *J. Amer. Chem. Soc.*, **83**, 1478 (1961).

(2) J. B. Wright, W. E. Dulin, and J. H. Markillie, *J. Med. Chem.*, **7**, 102 (1964).

(3) Marcel Harnik, U. S. Patent 3,096,327 (July 2, 1963).

(4) J. D. Park, H. A. Brown, and J. R. Lacher, *J. Amer. Chem. Soc.*, **75**, 4753 (1953).

(5) G. M. Everett and R. K. Richards, *J. Pharm. Exp. Ther.*, **81**, 402 (1944).

(6) G. M. Everett, L. E. Blockus, and I. M. Shepperd, *Science*, **124**, 79 (1956).

(7) C. H. Holten, *Acta Pharmacol. Toxicol.*, **13**, 113 (1957).

(8) B. Rubin, M. H. Malone, M. H. Waugh, and J. C. Burke, *J. Pharmacol. Exp. Ther.*, **120**, 125 (1957).

(9) T. Baum, D. K. Eckfeld, N. Metz, J. L. Dinish, G. Rowles, R. Van Pelt, A. T. Shropshire, S. P. Fernandez, S. P. Gluckman, I. Melvyn, and W. F. Bruce, *Experienta*, **25**, 1066 (1969).

(10) C. A. Winter, E. A. Riseley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).

(11) G. A. H. Buttle, P. F. D'Arcy, E. M. Howard, and D. N. Kellett, *Nature (London)*, **179**, 629 (1957).

(12) N. D. Levine, *Trans. Ill. State Acad. Sci.*, **13**, 233 (1950).

(13) C. P. Hegarty, R. Fagan, and T. S. Osdene, *Int. Congr. Chemother. Proc., 3rd.*, **1963**, 853 (1964).

(14) C. P. Hegarty, R. Fagan, and T. S. Osdene, *Ann. N. Y. Acad. Sci.*, **130**, 469 (1965).

(15) J. C. Reid and M. Calvin, *J. Amer. Chem. Soc.*, **72**, 2948 (1950).

CHART I
TRIFLUOROMETHYL PYRAZOLE DERIVATIVES

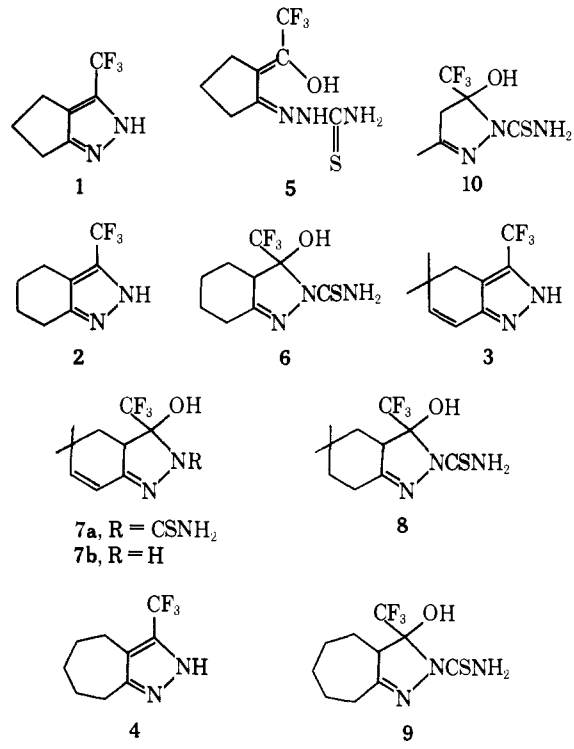


TABLE II
α-TRIFLUOROACETYL KETONES

Precursor of compd no.	% yield	Bp (mm), °C	Formula[a]
3, 7a, 7b	71	34–36 (0.1)	$C_{10}H_{11}F_3O_2$
8	24	31–33 (0.25)	$C_{10}H_{13}F_3O_2$

[a] *Anal.* C, H, F.

poured into H_2O, and the oily or solid material was collected, dried, and crystd to purity (see Table I).

3,4-Condensed-5-trifluoromethylpyrazoles. Method B.—The starting trifluoroacetyl ketone (0.025 mole) was dissolved in 50 ml of AcOH along with 5 ml (0.1 mole) of hydrazine hydrate and heated on the steam bath for 2 hr. Work-up was the same as described in method C.

5,5-Dimethyl-3-hydroxy-3-trifluoromethyl-3,3α,4,5-tetrahydroindazole (7b). Method C.—The starting trifluoroacetyl ketone (13.5 mmoles) was dissolved in 50 ml of 80% dioxane–H_2O and 2 ml (40 mmoles) of hydrazine hydrate was added. After standing 3 hr at room temp the sol was refrigerated overnight. The residual oil remaining after solvent removal at reduced pressure was extd into 5% NaOH, washed with Et_2O, acidified with 5% HCl, and extd back into Et_2O. Et_2O removal and recrystn from heptane gave **7b**.

2-(α,α,α-Trifluoro-β-hydroxyethylidene)cyclopentanone thiosemicarbazone was prepd and isolated as described in method B.

Antibacterial Screening.—The drug, in 1 ml of the appropriate dilu, was added to 9 ml of seed agar in sterile petri dishes. The hardened surface was inoculated with the test organism and incubated 18 hr at 35°. The end point, min inhibitory concn (MIC) in μg/ml was the least amt of drug that completely inhibited the test organism.

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Structure of the Diuretic Merbaphen

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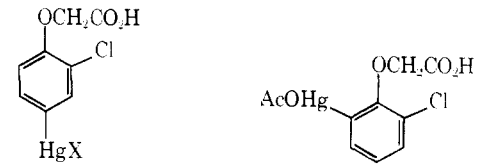
Although the clinical use of merbaphen has long since been abandoned, the compound is still of interest in structure–activity studies.[1] It was introduced as an antisyphilitic agent[2] but while being administered for that purpose it was found to have diuretic properties[3] greater than any drug then known. Thus it was demonstrated for the first time that profound diuresis could be induced by administration of a drug. This observation initiated a search for other potent, but less toxic, synthetic diuretics and so merbaphen became the predecessor of all the mercurial diuretics that followed and, in a sense, of the present-day potent nonmercurial diuretics. It is, therefore, surprising that the actual structure of merbaphen, apparently, never has been determined.

The chemical form of merbaphen used clinically is a combination formed with sodium diethylbarbiturate from the anhydro form[4] of the product that is obtained when 2-chlorophenoxyacetic acid is treated with $Hg(OAc)_2$.[5] It is obvious that the structure of the drug depends upon which of the 2 possible position isomers, Ia or II, is obtained in the mercuration reaction. In various papers and text books, structures of merbaphen are given which derive from Ia[6] or II.[7] No concrete evidence could be located to substantiate either structural assignment.



Since we were unable to obtain a sample of commercial merbaphen, we decided to remove, by synthetic procedures, the ambiguity surrounding its structure. To this end, 2-chloro-4-chloromercuriphenoxyacetic acid (Ib) was prepared by an unequivocal synthesis from 4-amino-2-chlorophenoxyacetic acid by the method of Weiner, *et al.*,[1] and compared with the chloromercuri compound obtained *via* the original mercuration procedure.[5]

The original method[5] of heating 2-chlorophenoxyacetic acid with $Hg(OAc)_2$ in H_2O gave the acetoxy-

(1) I. M. Weiner, R. I. Levy, and G. H. Mudge, *J. Pharmacol. Exp. Ther.*, **138**, 96 (1962).
(2) K. Zeiler, *Muenchen Med. Wochenschr.*, **64**, 1257 (1917).
(3) (a) P. Saxyl and R. Heilig, *Wien. Klin. Wochenschr.*, **33**, 943 (1920); (b) A. Vogel, *Amer. Heart J.*, **39**, 881 (1950).
(4) Bayer and Co., German Patent 264,267 (1912).
(5) Bayer and Co., German Patent 261,229 (1912).
(6) (a) E. C. White, *Ind. Eng. Chem.*, **16**, 1034 (1924); (b) J. H. Crawford and J. F. McIntosh, *J. Clin. Invest.*, **1**, 333 (1925); (c) "May's Chemistry of Synthetic Drugs," Longmans Green and Co., London, 1959, p 320; (d) Jenkins and Hartung, "Chemistry of Organic Medical Products," Wiley, New York, N. Y., 1949, p 507.
(7) (a) H. T. A. Haas, *Pharmazie*, **2**, 1 (1947); (b) J. G. Topliss, *Med. Chem.*, 979 (1970).