New Compounds

Derivatives of 2-Hydroxy-*p*-phenetidine. I. Azomethines[1]

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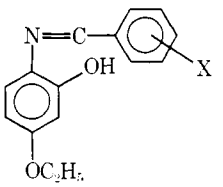
We have reported[2] an improved synthesis of 2-hydroxy-*p*-phenetidine. The *N*-acetyl derivative of this compound has recently been identified[3] as a toxic metabolite of *p*-acetophenetide (phenacetin) in the urine of cats, dogs, and humans. Since the azomethine linkage is not unknown, and even plays a role, in certain physiological reactions,[4] it occurred to us to prepare a series of compounds condensing this biologically interesting amine with various aryl aldehydes seeking compounds of possible therapeutic value. Twenty new compounds were made and are presented in Table I. Their ir spectra had a band at 1626–1618 cm^{-1} (C=N stretching).[5]

TABLE I
AZOMETHINE DERIVATIVES OF 2-HYDROXY-*p*-PHENETIDINE



Compound no.	X	Mp, °C	Yield,[a] %	Formula[b]
1	H[c]	109–110	90	$C_{15}H_{15}NO_2$
2	2-OH[c]	151–152	90	$C_{15}H_{15}NO_3$
3	3-OH[d]	137–138	46	$C_{15}H_{15}NO_3$
4	4-OH[c]	108–109	60	$C_{15}H_{15}NO_3$
5	3-OCH_3-4-OH[e]	136–137	95	$C_{16}H_{17}NO_4$
6	3,4-CH_2O_2[f]	131–132	61	$C_{16}H_{15}NO_4$
7	3,4-$(OCH_3)_2$[c]	114–115	84	$C_{17}H_{19}NO_4$
8	3,4,5-$(OCH_3)_3$[f]	118–119	69	$C_{18}H_{21}NO_5$
9	4-$NHCOCH_3$[c]	190–191	81	$C_{17}H_{18}N_2O_3$
10	4-$N(CH_3)_2$[e]	167–168	77	$C_{17}H_{20}N_2O_2$
11	2-NO_2[c]	104–105	49	$C_{15}H_{14}N_2O_4$
12	3-NO_2[c]	119–120	61	$C_{15}H_{14}N_2O_4$
13	4-NO_2[f]	147–148	70	$C_{15}H_{14}N_2O_4$
14	2-Cl[e]	85–86	53	$C_{15}H_{14}ClNO_2$
15	3-Cl[f]	97–98	68	$C_{15}H_{14}ClNO_2$
16	4-Cl[c]	125–126	65	$C_{15}H_{14}ClNO_2$
17	2,6-Cl_2[f]	111–112	63	$C_{15}H_{13}Cl_2NO_2$
18	3,4-Cl_2[c]	117–118	63	$C_{15}H_{13}Cl_2NO_2$
19	3,5-Cl_2[g]	104–105	83	$C_{15}H_{13}Cl_2NO_2$
20	H[c] [cinnamylidene]	115–116	57	$C_{17}H_{17}NO_2$

[a] Yield after one recrystallization (EtOH). [b] All of the compounds had correct analyses for C, H, and N (within 0.4% of the theoretical) except compound **13**: Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 62.70; H, 5.40; N, 9.85. All analyses were done by Dr. A. Bernhardt, Elbach über Engelskirchen, Germany. Aldehy deobtained from [c] The Matheson Co., Inc. [d] J. T. Baker Chemical Co. [e] Eastman Kodak Co. [f] Aldrich Chemical Co. [g] Synthesized in this laboratory by the method of H. S. Sharadamma, S. H. Kulkarni, P. B. Sattur, and K. S. Nargund, *J. Karnatak Univ.*, **1**, 61 (1956).

In addition to these azomethines, the parent amine and its *N*-acetyl derivative were tested in BDF_1 mice (with L1210 lymphoid leukemia) for antitumor activity by the Cancer Chemotherapy National Service Center, NCI. All of the compounds were inactive. It is of interest that whereas both 2-hydroxy-*p*-phenetidine and 2-hydroxy-*p*-acetophenetide were toxic at a dosage of 150 mg/kg (5/6 deaths with the amine, and 6/6 with the *N*-acetyl derivative), only one of the 20 azomethines caused a death at 400 mg/kg, the highest dose tested (**2**, Table I, 1 death of 6 mice tested).

Experimental Section[6]

The condensations between the amine and the various aldehydes were performed as described in the following procedure for ***N*-benzylidene-2-hydroxy-*p*-phenetidine.** To a hot (60°) solution of 7.6 g (0.05 mol) of 2-hydroxy-*p*-phenetidine in 50 ml of EtOH, 5.3 g (0.05 mol) of PhCHO was added slowly and the mixture was boiled for 10 min. Upon cooling to room temperature, a creamy white precipitate came out giving 15.5 g (95%), mp 109–110°. One recrystallization from EtOH gave an analytical sample with the same melting point.

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(2) M. J. Namkung and T. L. Fletcher, *J. Med. Chem.*, **12**, 348 (1969).
(3) A. Klutch, M. Harfenist, and A. H. Conney, *ibid.*, **9**, 63 (1966).
(4) D. E. Metzler, M. Ikawa, and E. E. Snell, *J. Amer. Chem. Soc.*, **76**, 648 (1954).
(5) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day Inc., San Francisco, Calif., 1962, p 222; The usual range given for C=N is 1690–1640 cm^{-1}, but this is shifted by the effects of conjugation. The spectra were run on a Beckman IR-5 instrument (KBr disks).
(6) Melting points were determined on a Fisher–Johns block and are corrected to standards.

2,3-Dihydro-4(1H)-quinazolinone Derivatives

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As a part of a search for 2,3-dihydro-4(1H)-quinazolinone compounds with possible pharmacological activity,[1] some potential antipyretic, hypotensive, and CNS depressant 3-aminoalkyl-2,3-dihydro- and 3-amino-2,3-dihydro-4(1H)-quinazolinone derivatives were prepared; moreover, a series of 3-hydroxy-2,3-dihydro-4(1H)-quinazolinone derivatives was synthesized as possible antibacterial[2] and antifungal agents on the basis of the known activity of some benzohydroxamic and cyclic hydroxamic acids (Table I).

(1) G. Bonola, P. Da Re, M. J. Magistretti, E. Massarani, and I. Setnikar, *J. Med. Chem.*, **11**, 1136 (1968).
(2) Bacteriostatic 3-hydroxy-2,3-dihydro-4(1H)-quinazolinones have been quite recently reported by Farbwerke Hoechst A.-G., Netherland Appl. 6,609,924 (1967); *Chem. Abstr.*, **68**, 59609 (1968).