Preparation and Properties of Some *N*-Aryl Hydroxamic Acids

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The preparation and properties of 27 *N*-aryl hydroxamic acids, of which 22 are reported for the first time, are described. The preparations are made by reacting *N*-aryl hydroxylamines with acid chlorides at low temperatures in ethereal solutions containing suspensions of sodium bicarbonate. The yields range from 50 to 90%. These compounds have been characterized in terms of analysis, melting point, and ultraviolet spectrum. These acids were synthesized for possible analytical applications.

THE preparation and properties of 22 *N*-aryl hydroxamic acids were reported recently (*3*). Further work on 25 *N*-aryl hydroxamic acids, of which 22 are reported for the first time, is described herein.

When an *N*-aryl hydroxylamine reacts with an acid chloride both of its hydrogen atoms, attached to the nitrogen and oxygen atoms, are attacked, thereby producing mono- and disubstituted hydroxamic acids. In the method reported previously (*3*), the experimental conditions were such as to produce appreciable amounts of the di-derivative. Hence, the desired mono-derivative had to be isolated from the crude product by tedious and repeated extractions with concentrated ammonium hydroxide, in which the di-derivative is insoluble, and subsequent acidification with hydrochloric acid (*3*). In the modified procedure adopted here, equimolar proportions of *N*-aryl hydroxylamines and acid chlorides were allowed to react at low temperatures—0 ° C. or lower—in an ether solution containing a suspension of aqueous sodium bicarbonate. Under these conditions, the product obtained contains a negligible amount of the diderivative and is readily purified by one or two crystallizations from suitable solvents. Using the modified procedure, improved yields of hydroxamic acids of higher purity have been effected.

The use of stoichiometric proportions of *N*-aryl hydroxylamines and acid chlorides is recommended. An excess of acid chloride generally results in increasing amounts of the di-derivative, whereas, the use of an excess of the *N*-aryl hydroxylamine leads to a product

Table I. Properties of Hydroxamic Acid

Compound No.	Hydroxamic Acid	Formula	Mol. Wt.	M.P., ° C.	U.V. Spectra		Calcd.			Found		
					λ_{max} (mμ)	10^{-3} ε	C	H	N	C	H	N
1	*N*-Phenyl-*n*-butyro-	$C_{10}H_{13}O_2N$	179.21	81[a]	252	9.8	67.02	7.31	7.82	67.30	7.20	7.66
2	*N*-*p*-Tolyl-*n*-butyro-	$C_{11}H_{15}O_2N$	193.24	63	252	11.1	68.37	7.82	7.25	68.50	7.90	7.40
3	*N*-Phenyllauro-	$C_{18}H_{29}O_2N$	291.42	80	251	10.1	74.18	10.03	4.81	74.10	10.10	5.00
4	*N*-*p*-Tolyllauro-	$C_{19}H_{31}O_2N$	305.45	80	251	10.8	74.71	10.23	4.59	74.70	10.20	4.53
5	*N*-Phenylpalmito-	$C_{22}H_{37}O_2N$	347.55	91	250	9.6	76.03	10.73	4.03	76.03	10.64	4.18
6	*N*-*p*-Tolylpalmito-	$C_{23}H_{39}O_2N$	361.57	85	250	9.6	76.40	10.87	3.87	76.61	10.85	3.96
7	*N*-Phenylphenylaceto-	$C_{14}H_{13}O_2N$	227.25	91[b]	251	10.8	73.99	5.77	6.16	74.20	5.80	6.28
8	*N*-*p*-Tolylphenylaceto-	$C_{15}H_{15}O_2N$	241.28	110	252	11.0	74.66	6.27	5.81	74.90	6.20	5.77
9	*N*-Phenylphenoxyaceto-	$C_{14}H_{13}O_3N$	243.27	154	251	9.0	69.11	5.39	5.75	69.09	5.21	5.70
10	*N*-Phenyl-*p*-chloro-phenoxyaceto-	$C_{14}H_{12}O_3NCl$	277.72	175	251 228	15.1 16.6	60.53	4.36	5.04[c]	60.46	4.45	4.95
11	*N*-Phenyl-*p*-fluorobenzo-	$C_{13}H_{10}O_2NF$	231.23	138	267	9.2	67.50	4.36	6.06	67.65	4.30	5.90
12	*N*-*p*-Tolyl-*p*-fluorobenzo-	$C_{14}H_{12}O_2NF$	245.26	150	268	10.7	68.55	4.93	5.70	68.50	5.00	5.85
13	*N*-*p*-Tolyl-*o*-chlorobenzo-	$C_{14}H_{12}O_2NCl$	261.72	139	258	10.7	64.25	4.62	5.35[d]	64.45	4.60	5.32
14	*N*-Phenyl-*o*-bromobenzo-	$C_{13}H_{10}O_2NBr$	292.15	113	256	10.4	53.45	3.43	4.80[e]	53.60	3.60	4.70
15	*N*-*p*-Tolyl-*o*-bromobenzo-	$C_{14}H_{12}O_2NBr$	306.17	130	258	11.1	54.93	3.95	4.57[f]	55.10	3.86	4.64
16	*N*-*p*-Tolyl-*m*-bromobenzo-	$C_{14}H_{12}O_2NBr$	306.17	88	271	10.3	54.93	3.95	4.57[g]	54.80	4.00	4.45
17	*N*-Phenyl-*p*-bromobenzo-	$C_{13}H_{10}O_2NBr$	292.15	160–4d	270	12.4	53.45	3.43	4.80[h]	53.35	3.50	4.68
18	*N*-*p*-Tolyl-*p*-bromobenzo-	$C_{14}H_{12}O_2NBr$	306.17	180d	272	12.9	54.93	3.95	4.57[i]	55.10	4.10	4.73
19	*N*-*p*-Tolyl-*o*-iodobenzo-	$C_{14}H_{12}O_2NI$	353.17	128	232	14.9	47.61	3.42	3.97[j]	47.68	3.24	4.02
20	*N*-Phenyl-*m*-methylbenzo-	$C_{14}H_{13}O_2N$	227.25	93	272	9.2	73.99	5.77	6.16	74.12	5.94	5.98
21	*N*-*p*-Tolyl-*m*-methylbenzo-	$C_{15}H_{15}O_2N$	241.29	112	272	9.2	74.67	6.27	5.80	74.82	6.10	5.60
22	*N*-*p*-Tolyl-*o*-methylbenzo-	$C_{15}H_{15}O_2N$	241.29	103	259	10.6	74.67	6.27	5.80	74.80	6.40	5.90
23	*N*-*p*-Tolyl-*p*-methylbenzo-	$C_{15}H_{15}O_2N$	241.29	119	270	10.50	74.67	6.27	5.80	74.80	6.30	5.62
24	*N*-Phenyl-*p*-methoxybenzo-	$C_{14}H_{13}O_3N$	243.27	130	273	15.00	69.11	5.39	5.75	69.36	5.45	5.58
25	*N*-*p*-Tolyl-*p*-methoxybenzo-	$C_{15}H_{15}O_3N$	257.31	129	275	13.90	70.00	5.88	5.44	69.85	5.77	5.32

[a] Reported, m.p., 76–77° C. (*2*). [b] Reported, m.p., 89–92° C. (*1*). [c] Calcd.: Cl, 12.76. Found: Cl, 12.85. [d] Calcd.: Cl, 13.55. Found: Cl, 13.38. [e] Calcd.: Br, 27.35. Found: Br, 27.50. [f] Calcd.: Br, 26.10. Found: Br, 26.13. [g] Calcd.: Br, 26.10. Found: Br, 26.00. [h] Calcd.: Br, 27.35. Found: Br, 27.22. [i] Calcd.: Br, 26.10. Found: Br, 26.33. [j] Calcd.: I, 35.94. Found: I, 36.10.

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which is badly contaminated. Presumably this contamination is due to the decomposition of the unreacted *N*-aryl hydroxylamine to complex products.

In general, the preparations are trouble-free when pyridine is replaced by aqueous suspensions of sodium bicarbonate. For comparison of yield and purity several hydroxamic acids reported previously (*3*) were prepared by the modified procedure. Use of aqueous suspensions of sodium bicarbonate gave white crystalline products instead of the light brown sticky products obtained before when pyridine was employed. Even ortho- and meta- substituted derivatives, which readily turned into oily forms when prepared by the previous method, were obtained in crystalline form and satisfactory yield.

At first glance, the use of aqueous suspensions of sodium bicarbonate may appear objectionable on ground of hydrolysis of acid chlorides. However, under the experimental conditions employed, the rate of hydrolysis of acid chlorides is extremely slow because diethyl ether which constitutes the reaction medium, is immiscible with water and is maintained at low temperature. Even aliphatic acid chlorides, which generally, hydrolyze much more readily than aromatic types, give satisfactory products.

The hydroxamic acids prepared in this study are summarized in Table I.

EXPERIMENTAL

Materials and Apparatus. The materials and apparatus have been described (*3*). All melting points were taken by the capillary method and are uncorrected. Ultraviolet absorption spectra of the hydroxamic acids were scanned on a Beckman Model DK-2 ratio recording spectrophotometer using two 10-mm. matched silica cells. The absorption measurements, made at constant wavelength for the calculation of molar absorptivity, ϵ, were performed on a Unicam SP 500 spectrophotometer. Molar absorptivity is expressed in units of liters per mole cm. All samples were dissolved in spectroscopic grade of 95% ethyl alcohol.

Procedure for Synthesis. One-tenth mole of freshly crystallized *N*-aryl hydroxylamine, dissolved in 150 ml. of diethyl ether, and a fine powder of 0.15 to 0.2 mole of sodium bicarbonate in 25 ml. of water, were mixed together and stirred mechanically with external cooling to bring the temperature to 0° C. or lower. A solution of 0.1 mole of appropriate acid chloride in 100 to 150 ml. of diethyl ether was added from a dropping funnel during the course of about an hour. Usually a granular, white precipitate was obtained, but in a few cases no solid product separated. The ethereal layer was separated and the ether removed under vacuum. Any solid matter thus obtained was combined with the bulk of the product, which was thoroughly triturated in a porcelain mortar with an excess of saturated solution of sodium bicarbonate for about 15 minutes to remove the acidic impurities. The solution was filtered, and the solid was washed with water and dried. The products were generally crystallized from a mixture of benzene and petroleum ether—in a few cases, when restricted by the limitations of solubility, from a mixture of ethyl alcohol and water—without the use of charcoal. Heating for prolonged periods in the solvent mixture should be avoided since discoloration of the product usually occurs. The yields of the hydroxamic acids ranged from 50 to 90%.

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17α-*n*-Propyl- and 17α-Isopropylestra-1,3,5(10)-triene-3,17β-diol

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THE PREPARATION of 17α-*n*-propyl- and 17α-isopropylestra-1,3,5(10)-triene-3,17β-diol was carried out in connection with studies concerned with the physiological activities of various estrogenic hormones.

The first two members of the homologous series, 17α-methylestra-1,3,5(10)-triene-3,17β-diol (*1*) and 17α-ethylestra-1,3,5(10)-triene-3,17β-diol (*2*) have been reported previously in the chemical literature.

EXPERIMENTAL

Melting points were taken in a modified Hershberg apparatus and are uncorrected. The microanalyses were carried out by Huffman Microanalytical Laboratories, Wheatridge, Colo.

17α-*n*-Propylestra-1,3,5(10)-triene-3,17β-diol (I). To 8.6 grams of Mg turnings suspended in 100 ml. of absolute ether was added at 1° C. with vigorous stirring 15 to 20 ml. of a solution of 38.8 grams of allyl bromide in 290 ml. of ether. The reaction started immediately, and the temperature rose to 21° C. After cooling to 3° C., the main amount of the reagent solution was added during 1¼ hours and the mixture stirred an additional 1½ hours at 0 to 4° C. To this solution was added over 1 hour, 7.03 grams of 3-benzyloxyestra-

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