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Some Derivatives of 2-(*p*-Aminoaryl)-2-arylethylamines

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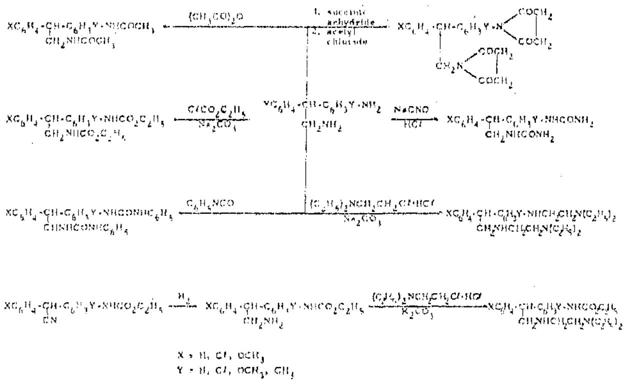
The *N,N'*-diacetyl, *N,N'*-disuccinyl, *N,N'*-dicarbethoxy, *N,N'*-dicarbamyl, *N,N'*-bis-(phenylcarbamyl), *N,N'*-bis(2'-diethylaminoethyl), *N'*-carbethoxy, and *N'*-carbethoxy-N-(2''-diethylaminoethyl) derivatives of some 2-(*p*-aminoaryl)-2-arylethylamines are described.

THE compounds reported here were prepared as part of an investigation of the chemical behavior of the 2-(*p*-aminoaryl)-2-arylethylamines and for submission to physiological testing programs. The diarylethylamines employed have been previously described (*2*).

The *N,N'*-diacetyl derivatives of the 2-(*p*-aminoaryl)-2-arylethylamines were prepared by the reaction of these amines with acetic anhydride following a procedure similar to that of Vogel (*6*). The corresponding *N,N'*-disuccinyl substituted compounds were obtained by treating the amines with succinic anhydride, followed by treatment with acetyl chloride according to the methods of Fieser (*4*). The *N,N'*-dicarbethoxy analogs were synthesized by way of the procedure of Damschroeder and Shriner (*1*). The *N,N'*-bis(phenylcarbamyl) derivatives were prepared by adding two molar equivalents of phenyl isocyanate to solutions containing one molar equivalents of the 2-(*p*-aminoaryl)-2-arylethylamines in tetrahydrofuran. These reaction mixtures were heated at reflux for one-half hour and then allowed to cool, whereupon the products precipitated. The *N,N'*-bis(2''-diethylaminoethyl) substituted amines were obtained by the reaction of the amines with 2-diethylaminoethyl chloride hydrochloride and sodium carbonate according to the method of Peak and Watkins (*5*). They were isolated and purified as salts.

The 2-(*p*-*N*-carbethoxyaminoaryl)-2-arylethylamines were prepared by the Raney nickel catalyzed reduction of the corresponding *p*-*N*- carbethoxyaminoarylarylacetonitriles, previously described (*3*), in tetrahydrofuran with an initial hydrogen pressure of about 1000 p.s.i.g. in a suitable reaction vessel with rocking, and heated at about 50° to 80° C. for 1 to 2 hours. Some of the products were isolated and purified as salts. The 2-(*p*-*N*-carbethoxyaminoaryl)-2-arylethylamines were then converted to the 2-(*p*-*N*-carbethoxyaminoaryl) -2- aryl -*N*- (2'-diethylaminoethyl)ethylamines using 2-diethylaminoethyl chloride hydrochloride and potassium carbonate following the procedure of Peak and Watkins (*5*). These products were isolated and purified as salts.

The transformations of this investigation can be pictured by the following reaction schemes. Table I lists the compounds which were isolated and identified. Structures of the products were assigned on the basis of elemental analyses, infrared spectral data, and similarity in the reactions involved to known transformations.



The infrared spectra were obtained using solutions of the derivatives in chloroform of those compounds which were reasonably soluble in chloroform. For the other derivatives, the spectra were obtained using mulls in Nujol or potassium bromide disks. As for compounds initially isolated as oils, infrared spectra were obtained both for the oils and the purified salts. All derivatives showed at least some modification of the amino absorption bands in the 2.8- to 3.0-micron region in comparison with the spectra of the underivatized compounds. Typical carbonyl absorption bands were in the 5.6- to 6.1-micron region of the spectra of all derivatives except the *N,N'*-bis(2''-diethylaminoethyl) derivatives. However, the salts of the latter did show typical carbonyl peaks. In addition, all salts showed characteristic broad bands in the 3.0- to 4.0-micron region. The *N,N'*-disuccinyl compounds showed no nitrogen to hydrogen absorption in the 2.8- to 3.0-micron region.

Table I. Derivatives of 2-(*p*-Aminoaryl)-2-arylethylamines

Compound	M.P., °C.^{a}	Yield, %	Solvent^b	Analysis, %^{c}			
				C	H	N	Cl
N,N′-Diacetyl-2-(4′-aminophenyl)-2-phenylethylamine	90–1	79	1–2	72.95 72.74	6.80 6.98		
N,N′-Diacetyl-2-(4′-amino-3′-methylphenyl)-2-phenylethylamine	162–4	76	3	73.52 73.29	7.14 7.14		
N,N′-Diacetyl-2-(4′-aminophenyl)-2-(4′-chlorophenyl)ethylamine	152–4	91	1–3	65.35 65.58	5.79 5.84		
N,N′-Diacetyl-2-(4′-aminophenyl)-2-(4′-methoxyphenyl)ethylamine	149–51	94	1–2	69.91 69.70	6.80 6.95		
N,N′-Disuccinyl-2-(4′-aminophenyl)-2-phenylethylamine	202–04	82	1–4	70.20 69.97	5.63 5.52		
N,N′-Disuccinyl-2-(4′-amino-3′-methylphenyl)-2-phenylethylamine	213–15	84	1	70.75 70.63	5.68 5.89		
N,N′-Disuccinyl-2-(4′-amino-3′-chlorophenyl)-2-phenylethylamine	212–14	79	1	64.31 64.81	4.66 5.11		8.63 8.35
N,N′-Disuccinyl-2-(4′-amino-3′-methoxyphenyl)-2-phenylethylamine	220–2	76	1–4	67.97 67.51	5.46 5.61		
N,N′-Disuccinyl-2-(4′-aminophenyl)-2-(4′-chlorophenyl)ethylamine	203–05	81	1	64.31 64.11	4.66 4.78		8.63 8.43
N,N′-Disuccinyl-2-(4′-aminophenyl)-2-(4′-methoxyphenyl)ethylamine	208–10	78	1–4	67.97 67.76	5.46 5.49		
N,N′-Dicarbethoxy-2-(4′-aminophenyl)-2-phenylethylamine	92–4	76	5	67.39 67.62	6.79 6.75	7.86 8.07	
N,N′-Dicarbethoxy-2-(4′-amino-3′-methoxyphenyl)-2-phenylethylamine	69	87	6	65.27 65.17	6.78 6.71	7.25 7.16	
N,N′-Dicarbethoxy-2-(4′-aminophenyl)-2-(4′-chlorophenyl)ethylamine	106	90	2–5	61.46 61.57	5.93 5.88		9.07 9.30
N,N′-Dicarbethoxy-2-(4′-aminophenyl)-2-(4′-methoxyphenyl)ethylamine	53–5	95	3–6	65.27 65.50	6.78 7.03	7.25 7.20	
N,N′-Dicarbamyl-2-(4′-aminophenyl)-2-phenylethylamine	207–09	48	5	64.41 64.42	6.08 6.27	18.78 18.36	
N,N′-Dicarbamyl-2-(4′-amino-3′-methylphenyl)-2-phenylethylamine	218–20	52	5	65.36 65.17	6.46 6.48	17.36 17.30	
N,N′-Dicarbamyl-2-(4′-amino-3′-methoxyphenyl)-2-phenylethylamine	177	71	2	62.18 62.00	6.41 6.27	17.06 16.98	
N,N′-Dicarbamyl-2-(4′-aminophenyl)-2-(4′-chlorophenyl)ethylamine	179–81	46	2	57.74 57.94	5.15 5.29	16.84 16.90	
N,N′-Dicarbamyl-2-(4′-aminophenyl)-2-(4′-methoxyphenyl)ethylamine	191–3	49	2	62.18 62.18	6.14 6.18	17.06 17.17	
N,N′-Bis(phenylcarbamyl)-2-(4′-aminophenyl)-2-phenylethylamine	196–8	73	7	74.64 74.45	5.82 6.11		
N,N′-Bis(phenylcarbamyl)-2-(4′-amino-3′-methylphenyl)-2-phenylethylamine	227–8	78	7	74.98 75.02	6.07 6.36		
N,N′-Bis(phenylcarbamyl)-2-(4′-amino-3′-chlorophenyl)-2-phenylethylamine	205–06	91	7	69.34 69.49	5.20 5.38		
N,N′-Bis(phenylcarbamyl)-2-(4′-amino-3′-methoxyphenyl)-2-phenylethylamine	225–6	89	7	72.48 72.00	5.87 6.10		
N,N′-Bis(phenylcarbamyl)-2-(4′-aminophenyl)-2-(4′-chlorophenyl)ethylamine	217–18	95	7	69.34 69.21	5.20 5.34		
N,N′-Bis(phenylcarbamyl)-2-(4′-aminophenyl)-2-(4′-methoxyphenyl)ethylamine	225–6	94	7	72.48 72.38	5.87 6.18		
N,N′-Bis(2′-diethylaminoethyl)-2-(4′-aminophenyl)-2-phenylethylamine trioxalate salt monohydrate	96–100	75^d	5	55.00 55.25	7.21 7.43	8.02 8.30	
N,N′-Bis(2′-diethylaminoethyl)-2-(4′-amino-3′-methylphenyl)-2-phenylethylamine trioxalate salt	131–4	73^d	5	57.05 56.93	7.25 7.29	8.06 7.86	
N,N′-Bis(2′-diethylaminoethyl)-2-(4′-amino-3′-chlorophenyl)-2-phenylethylamine trioxalate salt	126–8	84^d	5	53.74 53.87	6.63 6.80		4.96 5.23
N,N′-Bis(2′-diethylaminoethyl)-2-(4′-amino-3′-methoxyphenyl)-2-phenylethylamine trioxalate salt	109–11	71^d	5–8	55.76 55.67	7.09 7.22	7.87 7.52	
N,N′-Bis(2′-diethylaminoethyl)-2-(4′-aminophenyl)-2-(4′-chlorophenyl)ethylamine trioxalate salt	108–12	74^d	5	53.74 54.06	6.63 6.84	7.83 7.63	
N,N′-Bis(2′-diethylaminoethyl)-2-(4′-aminophenyl)-2-(4′-methoxyphenyl)ethylamine trioxalate salt monohydrate	112–15	66^d	5	54.38 54.67	7.19 7.21	7.69 7.48	
N′-Carbethoxy-2-(4′-aminophenyl)-2-phenylethylamine	94–5	85	3–6	71.80 71.96	7.09 7.19	9.85 9.98	
N′-Carbethoxy-2-(4′-amino-3′-methylphenyl)-2-phenylethylamine hemifumarate salt	181	69^d	5–8	67.39 67.11	6.79 6.88	7.86 8.06	
N′-Carbethoxy-2-(4′-amino-3′-chlorophenyl)-2-phenylethylamine hemifumarate salt	169	84^d	5–8	60.55 60.47	5.62 6.01	7.44 7.21	
N′-Carbethoxy-2-(4′-amino-3′-methoxyphenyl)-2-phenylethylamine monofumarate salt	174	52^d	5–8	61.38 61.25	6.09 6.10	6.51 6.48	
N′-Carbethoxy-2-(4′-aminophenyl)-2-(4′-chlorophenyl)ethylamine hemifumarate salt	155	78^d	9	60.55 60.28	5.62 5.90	7.44 7.33	

(*Continued*)

Table I. Derivatives of 2-(*p*-Aminoaryl)-2-arylethylamines (*Continued*)

Compound	M.P., °C.[a]	Yield, %	Solvent[b]	Analysis, %[c] C	H	N	Cl
N′-Carbethoxy-2-(4′-aminophenyl)-2-(4′-methoxyphenyl)ethylamine monooxalate salt	95–7	84[d]	3–7	59.39 59.11	5.98 6.22	6.93 6.71	
N′-Carbethoxy-*N*-(2′-diethylaminoethyl)-2-(4′-aminophenyl)-2-phenylethylamine dioxalate salt	190–3	41[d]	5	57.53 57.18	6.62 6.87	7.45 7.34	
N′-Carbethoxy-*N*-(2′-diethylaminoethyl)-2-(4′-amino-3′-methylphenyl)-2-phenylethylamine dioxalate salt	177–8	57[d]	5–8	58.22 57.92	6.80 6.90	7.28 6.91	
N′-Carbethoxy-*N*-(2′-diethylaminoethyl)-2-(4′-amino-3′-chlorophenyl)-2-phenylethylamine dioxalate salt monohydrate	170	42[d]	5	52.62 52.45	6.21 6.23	6.82 6.53	
N′-Carbethoxy-*N*-(2′-diethylaminoethyl)-2-(4′-amino-3′-methoxyphenyl)-2-phenylethylamine dioxalate salt	165	83[d]	9	56.65 56.39	6.62 6.63	7.08 7.00	
N′-Carbethoxy-*N*-(2′-diethylaminoethyl)-2-(4′-amino phenyl)-2-(4′-chlorophenyl)ethylamine dioxalate salt	169	57[d]	9	54.22 54.18	6.07 5.94	7.03 7.22	
N′-Carbethoxy-*N*-(2′-diethylaminoethyl)-2-(4′-aminophenyl)-2-(4′-methoxyphenyl)ethylamine dioxalate salt monohydrate	180–1	62[d]	5	54.98 54.87	6.76 7.05	6.87 7.08	

[a] Melting points were determined using a copper block and are uncorrected. [b] Recrystallization solvents used: 1. methanol, 2. water, 3. benzene, 4. chloroform, 5. ethanol, 6. petroleum ether (b.p. 60 to 71° C.), 7. tetrahydrofuran, 8. ethyl acetate, 9. isopropyl alcohol. Where two numbers are indicated, co-solvents were used. [c] Analyses by Midwest Microlab, Inc., Indianapolis, Ind. First series calculated, second found. [d] Yield includes the step of salt formation.

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Thermodynamic Studies of Hydrochloric Acid in Tetrahydrofuran-Water Mixtures

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The cell, Pt, H_2(1 atm.) | HCl(*m*), tetrahydrofuran (*X*), water (*Y*) | Agcl, Ag, has been used to investigate the thermodynamic properties of hydrochloric acid. Activity coefficients, medium effects, relative partial molal heat contents, and heat capacities for *X* = 8.98, 18.21, 47.20, 73.03, and 89.00 weight % tetrahydrofuran at various temperatures have been calculated.

THE ultimate purpose of our research program is to investigate the effect of the solvent on the thermodynamics of chemical equilibria (*1, 6, 13*). Hydrochloric acid appeared to be the most natural first choice as the system to study, aimed at finding an analytical function for the so-called medium effects.

To calculate the thermodynamic properties of hydrochloric acid in aqueous-organic mixed solvents (*2–5, 8–9*), the standard potential (*12*) of the reversible cell Pt, H_2 (1 atm.) | HCl (m), THF (X), H_2O (Y)| AgCl, Ag, was evaluated by a polynomial curve-fitting program. The cell was used to determine the activity coefficients, medium effects, relative partial molal heat contents, and relative partial molal heat capacities of hydrochloric acid for five different systems and at four different temperatures. This paper also describes the means of converting the values obtained from the mixed-solvent systems to those of the standard reference aqueous state by computational technique. The primary and secondary medium effects (*10*) are calculated in tetrahydrofuran (THF)-water (*11*) and 1,2-dimethoxyethane–water (*7*) mixtures.

THEORY

The mean activity coefficients of hydrochloric acid in the mixed solvents were calculated from the following rearranged Nernst equation:

$$\ln \gamma_{\pm} = \frac{{}^{S}E^{0} - [{}^{S}E + (2RT/F) \ln m]}{(2RT/F)} \qquad (1)$$

in which ${}^{S}E^{0}$ is the standard potential in the mixed solvent and ${}^{S}E$ corresponds to E_{obsd} (*4*)—i.e., the potential corrected to a hydrogen pressure of 1 atm.

The primary medium effect is considered to be due to the difference in the solution energies in two different solvents and also is a measure of the energy involved in the transfer of an ion at an infinite dilution in one solvent to an infinite dilution of another solvent. This effect (log ${}^{s}_{w}\gamma^{0}_{\pm}$ HCl) of tetrahydrofuran–water mixtures upon hydrochloric acid was calculated from the equation:

$$({}^{w}E^{0} - {}^{S}E^{0}) = \underset{m \to 0}{Lt} \left[\frac{4.606\,RT}{F} \log {}^{S}_{w}\gamma_{\pm} \right] = \frac{4.606RT}{F} \log {}^{S}_{w}\gamma^{0}_{\pm} \qquad (2)$$

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