New Biphenyl Derivatives I: 1-(4-Biphenylyl)-2-phenylethylamines as Potential Antispasmodic and Cardiovascular Agents

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Abstract □ A series of 1-(4-biphenylyl)-2-phenylethylamine derivatives was synthesized as potential antispasmodic and cardiovascular agents related to papaverine. Preliminary pharmacological tests, on isolated guinea pig ileum and anesthetized cat blood pressure, showed that the new compounds possess nonspecific inhibitory action on smooth muscles.

Keyphrases □ Biphenyl derivatives, various—synthesized, evaluated for antispasmodic and cardiovascular activity □ 2-Phenylethylamines, substituted—synthesized, evaluated for antispasmodic and cardiovascular activity □ Antispasmodic activity—various substituted 1-(4-biphenylyl)-2-phenylethylamines evaluated □ Cardiovascular activity—various substituted 1-(4-biphenylyl)-2-phenylethylamines evaluated □ Structure–activity relationships—various substituted 1-(4-biphenylyl)-2-phenylethylamines evaluated for antispasmodic and cardiovascular activity

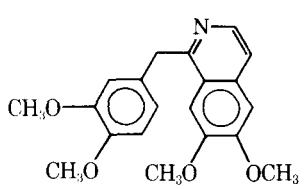
The fact that papaverine (I) has a partially dehydrogenated 1,2-diphenylethylamine (II) moiety in its structure initiated the preparation of some derivatives of II to investigate their biological activities.

Although some investigators (1–8) synthesized substituted II derivatives as possible analgesic agents, the 1-biphenylyl or 2-biphenylyl analogs have not been prepared. The present work dealt with the synthesis of some *N*-alkyl and *N*,*N*-dialkyl derivatives of 1-(4-biphenylyl)-2-phenylethylamine (VI, Scheme I) to determine whether they possessed antispasmodic and/or cardiovascular effects similar to I. The synthesized compounds are listed in Tables I and II.

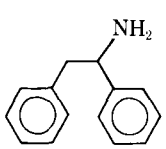
RESULTS AND DISCUSSION

Synthesis—The synthetic route (Scheme I) began with the preparation of benzyl 4-biphenylyl ketone (III) from phenylacetyl chloride and biphenyl by applying Friedel–Crafts conditions. The key intermediate, 1-(4-biphenylyl)-2-phenylethylamine (VI), was obtained either by the reduction of benzyl 4-biphenylyl ketoxime (IV) with aluminum amalgam in aqueous ethanol or from III through a modified Leuckart–Wallach reaction, *i.e.*, by first isolating the *N*-formyl derivative (V) followed by hydrolysis with concentrated hydrochloric acid.

The *N*-alkyl (IX) and *N*,*N*-dialkyl (XI) derivatives were prepared from the corresponding *N*-acyl (V and VIII) and *N*-acyl-*N*-alkyl (X) analogs, respectively, by reduction with lithium aluminum hydride in absolute ether. The *N*-methyl-*N*-propyl (XI*d*) and *N*,*N*-dimethyl (XI*e*) derivatives also were obtained through the Clarke–Eschweiler reaction by refluxing with a mixture of formaldehyde solution and formic acid. In addition, the *N*-benzoyl (VIII*c*) and *N*-benzoyl-*N*-methyl (X*f*) derivatives were prepared, but attempts to obtain the *N*-benzyl analogs through reduction with lithium aluminum hydride in absolute ether or absolute tetrahydrofuran were unsuccessful.



I



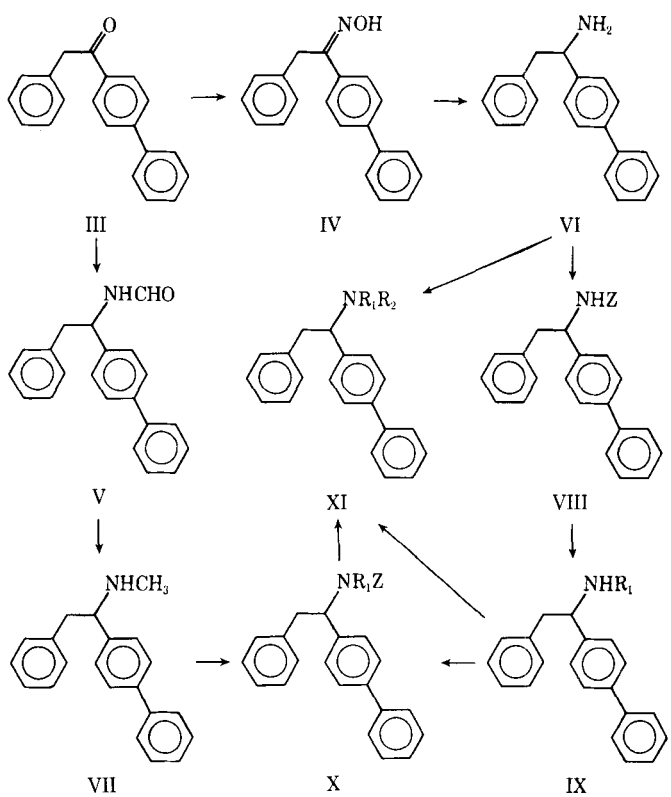
II

The structures of the new compounds were substantiated by IR, PMR, and mass spectrometric studies of representative members of the series. The mass spectrum of the *N*-acetyl derivative (VIII*a*) showed, in addition to the molecular ion peak, significant fragment ion peaks at *m/e* 314 (M − H), 272 (M − CH_3CO), 258 (M − CH_3CONH), 224 (M − $CH_2C_6H_5$), 182 (M − CH_3CO − $CH_2C_6H_5$ + H, base peak), 181 (M − CH_3CO − $CH_2C_6H_5$), and 180 (M − CH_3CO − $CH_2C_6H_5$ − H) and the biphenyl radical peak at 153.

Pharmacology—Testing of the antispasmodic activity of VII, IX*a*, XI*a*, XI*b*, XI*d*, and XI*e* was carried out on isolated guinea pig ileum. All of these compounds inhibited contractions produced by standard submaximal doses of acetylcholine, histamine, or serotonin with no specificity toward any of these spasmogens. The results showed that the tested compounds might possess considerable nonspecific inhibitory action on smooth muscles similar to I (9, 10).

A comparative study of XI*b*, XI*d*, and XI*e* with similar molar concentrations of I was then conducted. The data (Table III) indicated that the *N*,*N*-diethyl (XI*b*) and the *N*,*N*-dimethyl (XI*e*) analogs were more potent smooth muscle inhibitors than I, as shown by their antagonistic effects on acetylcholine-induced contractions.

The cardiovascular activity of IX*a*, XI*a*, XI*b*, XI*d*, and XI*e* was examined using the blood pressure response of chloralose–urethan anesthetized cats. The compounds were injected into the femoral vein, and the blood pressure was recorded from the carotid artery. The experiments revealed a marked hypotensive activity for all tested compounds; the most



Scheme I

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Table I—*N*-Acyl-1-(4-biphenylyl)-2-phenylethylamines and *N*-Acyl-*N*-alkyl-1-(4-biphenylyl)-2-phenylethylamines

Compound	Z	R_1	Method	Yield, %	Melting Point	Formula	Analysis, %	Calc.	Found
V	—	—	—	65	197–198°[a]	$C_{21}H_{19}NO$	C	83.7	84.0
							H	6.4	6.7
							N	4.6	4.6
VIII*a*	$COCH_3$	—	C	98	204–205°[a]	$C_{22}H_{21}NO$	C	83.8	84.2
							H	6.7	6.3
							N	4.4	4.7
VIII*b*	COC_2H_5	—	D	70	191–192°[a]	$C_{23}H_{23}NO$	C	83.9	84.3
							H	7.0	7.4
							N	4.3	4.7
VIII*c*	COC_6H_5	—	E,F[b]	60, 70	203–205°[c]	$C_{27}H_{23}NO$	C	85.9	86.1
							H	6.1	6.0
							N	3.7	4.2
X*a*	$COCH_3$	CH_3	C	70	130–131°[d]	$C_{23}H_{23}NO$	C	83.9	83.8
							H	7.0	7.0
							N	4.3	4.6
X*b*	$COCH_3$	C_2H_5	C	60	97–98°[d]	$C_{24}H_{25}NO$	C	83.9	83.8
							H	7.3	6.8
							N	4.1	4.5
X*c*	$COCH_3$	n-C_3H_7	C	50	85–87°[e]	$C_{25}H_{27}NO$	C	84.0	83.6
							H	7.6	7.2
							N	3.9	3.9
X*d*	COC_2H_5	CH_3	D	50	112–113°[e]	$C_{24}H_{25}NO$	N	4.1	4.4
X*e*	COC_2H_5	C_2H_5	D	55	217–218°[f]	$C_{25}H_{27}NO$	C	84.0	84.3
							H	7.6	7.5
							N	3.9	4.3
X*f*	COC_6H_5	CH_3	E	50	93–95°[e]	$C_{28}H_{25}NO$	C	85.9	86.2
							H	6.4	6.3
							N	3.6	3.5

[a] Recrystallized from ethanol. [b] Admixture of the products obtained by both methods showed no melting-point depression. [c] Recrystallized from methanol. [d] Recrystallized from petroleum ether (bp 40–60°). [e] Recrystallized from a benzene–petroleum ether mixture (bp 40–60°). [f] Recrystallized from benzene.

pronounced effect was produced by XI*b*. This effect could not be blocked by atropine, which indicated that it was not mediated through cholinergic nerve fibers but might have been due to a direct vasodilating effect on smooth muscles, an effect similar to that known for I (9, 10).

EXPERIMENTAL[1]

Benzyl 4-Biphenylyl Ketone (III)—Under strictly anhydrous conditions, a stirred mixture of biphenyl (15.4 g, 0.1 mole), carbon disulfide (300 ml), and finely powdered anhydrous aluminum chloride (24 g, 0.18 mole) was treated with phenylacetyl chloride (15.4 g, 0.1 mole). The reaction mixture was then refluxed at 50–60° for 6–8 hr. The carbon disulfide was then removed by distillation under reduced pressure, and the residue was decomposed with ice and dilute hydrochloric acid. The solid was triturated with ether, filtered, and recrystallized from ethanol to yield 19.6 g (72%) of product, mp 152–153° [lit. (11) mp 149°, yield 34%]. The IR spectrum showed a peak at 1690 cm^{-1}, indicative of a carbonyl group.

Benzyl 4-Biphenylyl Ketoxime (IV)—A solution of III (2.7 g, 0.01 mole) in ethanol (30 ml) was treated with a solution of hydroxylamine hydrochloride (1.4 g, 0.02 mole) in water (1 ml), followed by a solution of sodium hydroxide (2 g, 0.05 mole) in water (2 ml). The reaction mixture was then refluxed for 5 min, cooled, and poured into 2 *N* HCl (40 ml) with constant stirring. The solid product was filtered, washed several times with distilled water, dried, and recrystallized from methanol. The yield was 2.3 g (83%), mp 163–164°. The IR spectrum showed a broad peak centered at 3500 cm^{-1}, indicative of a hydroxyl group, a peak at 1650 cm^{-1}, indicative of C=N, and a peak at 950 cm^{-1}, indicative of NO.

Anal.—Calc. for $C_{20}H_{17}NO$: C, 83.6; H, 6.0; N, 4.9. Found: C, 83.8; H, 6.0; N, 4.4.

***N*-Formyl-1-(4-biphenylyl)-2-phenylethylamine (V)**—A mixture of III (2.7 g, 0.01 mole) and ammonium formate (2.5 g, 0.04 mole) was fused at 200–220° in an oil bath for 4–6 hr until frothing ceased. The reaction mixture was cooled to room temperature, triturated twice with water, and decanted. The residue was then extracted twice with benzene, and the combined extract was dried over anhydrous sodium sulfate and filtered. The solvent was then removed under reduced pressure, and the product was recrystallized.

1-(4-Biphenylyl)-2-phenylethylamine Hydrochloride (VI)—*Method A*—A solution of 5% aqueous mercuric chloride (100 ml) was added to aluminum foil (6 g) that had been cut into pieces of approximately 2 cm^2. The foil was left in contact with the mercuric chloride solution for 5–10 min to effect amalgamation and then washed with 3 × 250 ml of distilled water. The aluminum amalgam was treated immediately with a solution of IV (2.9 g, 0.01 mole) in ethanol (60 ml), followed by distilled water (60 ml).

The reaction mixture was magnetically stirred at room temperature for 24 hr and then filtered. The solid material on the filter was washed with 2 × 100 ml of ethanol, and the washings were added to the original filtrate. The alcohol was then removed under reduced pressure, and the product was extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate and filtered, and then dry hydrogen chloride gas was slowly bubbled through it. The separated salt was collected and recrystallized.

Method B—A solution of V (3 g, 0.01 mole) in ethanol (20 ml) was treated with concentrated hydrochloric acid (6 ml). The mixture was refluxed for 30 min and then allowed to cool to room temperature. The separated product was collected and recrystallized.

***N*-Acyl-1-(4-biphenylyl)-2-phenylethylamines and *N*-Acyl-*N*-alkyl-1-(4-biphenylyl)-2-phenylethylamines**—*Method C* (*VIII*a, X*a*, X*b*, *and* X*c*)—A mixture of the appropriate amine (VI, VII, IX*a*, and IX*b*, respectively) (0.01 mole), acetic anhydride (6 ml), and anhydrous sodium acetate (0.012 mole) was refluxed for 2 hr. The reaction mixture was allowed to cool to room temperature, poured onto crushed ice, and then neutralized by the addition of solid sodium bicarbonate in portions until effervescence ceased. The acetyl derivative was filtered, washed several times with hot distilled water, dried, and then recrystallized.

Method D (*VIII*b, X*d*, *and* X*e*)—A solution of propionyl chloride (0.015 mole) in benzene (10 ml) was added dropwise to a cooled, magnetically stirred solution of the appropriate amine (VI, VII, and X*a*, respectively) (0.01 mole), in pyridine (10 ml). Cooling was maintained for 2 hr, and then the reaction mixture was refluxed for another 4 hr. The solvents were removed *in vacuo*, and the resulting residue was treated with distilled water (30 ml), filtered, dried, and recrystallized.

Method E (*VIII*c *and* X*f*)—Benzoyl chloride (0.012 mole) was added to a mixture of the appropriate amine (VI and VII, respectively) (0.01 mole), and 4% NaOH (15 ml). The reaction mixture was vigorously shaken for 15 min and then acidified with 10% HCl. The product was filtered, washed several times with distilled water, dried, and recrystallized.

[1] IR spectra were determined on a Beckman IR-33 spectrophotometer with potassium bromide pellets. PMR spectra were determined on a Jeolco C-60 HL spectrometer with tetramethylsilane as the internal standard. The mass spectrum was determined using a du Pont-CEC 492 spectrometer. Melting points were determined in open glass capillaries and are uncorrected. Microanalyses were performed by the Microanalytical Unit, Faculty of Science, University of Cairo, Cairo, A.R. Egypt.

Table II—1-(4-Biphenylyl)-2-phenylethylamine and Its *N*-Alkyl and *N,N*-Dialkyl Derivatives

Compound	R_1	R_2	Yield[a], %	Melting Point	Formula	Analysis, %	Calc.	Found
VI	—	—	60[b], 70[c,d]	273°[e]	$C_{20}H_{20}ClN$	C	77.5	77.4
						H	6.5	6.8
						Cl	11.4	11.0
						N	4.5	4.1
VII	—	—	67	241–242°[e]	$C_{21}H_{22}ClN$	C	77.8	77.6
						H	6.8	7.0
						Cl	11.0	11.2
						N	4.3	4.7
IX*a*	C_2H_5	—	65	270°[e]	$C_{22}H_{24}ClN$	C	78.2	78.6
						H	7.2	6.9
						Cl	10.5	10.9
						N	4.1	4.3
IX*b*	n-C_3H_7	—	75	242–243°[e]	$C_{23}H_{26}ClN$	C	78.5	78.3
						H	7.7	7.6
						Cl	10.1	10.4
						N	4.0	4.5
XI*a*	CH_3	C_2H_5	64	136° dec.[f]	$C_{23}H_{26}ClN$	C	78.5	78.8
						H	7.7	7.7
						Cl	10.1	10.3
						N	4.0	4.0
XI*b*	C_2H_5	C_2H_5	60	166–167° dec.[g]	$C_{24}H_{28}ClN$	C	78.8	79.1
						H	7.7	8.0
						Cl	9.7	9.6
						N	3.8	3.5
XI*c*	C_2H_5	n-C_3H_7	70	167–169° dec.[h]	$C_{25}H_{30}ClN$	C	79.0	79.5
						H	8.0	7.8
						Cl	9.3	9.7
						N	3.7	4.0
XI*d*	CH_3	n-C_3H_7	70, 98[i,d]	196–198° dec.[g]	$C_{24}H_{28}ClN$	C	78.8	78.5
						H	7.7	7.3
						Cl	9.7	10.2
						N	3.8	4.1
XI*e*	CH_3	CH_3	80[i]	239–240°[f]	$C_{22}H_{24}ClN$	C	78.2	78.5
						H	7.2	7.3
						Cl	10.5	10.7
						N	5.1	4.6

[a] Unless otherwise indicated, Method G was used for preparation. [b] Method A. [c] Method B. [d] Admixture of the products obtained by both methods showed no melting-point depression. [e] Recrystallized from ethanol. [f] Recrystallized from a methanol–benzene mixture. [g] Recrystallized from an ethanol–benzene mixture. [h] Recrystallized from an ethanol–ether mixture. [i] Method H.

Method F (VIIIc)—A solution of benzoyl chloride (0.012 mole) in dry benzene (10 ml) was added dropwise to a cooled, magnetically stirred solution of VI (0.01 mole) in pyridine (10 ml). Cooling was maintained for 2 hr, and then the reaction mixture was refluxed for 4 hr. The solvents were removed under reduced pressure, and the residue was treated with water (30 ml), filtered, dried, and recrystallized.

IR spectra of VIII*a*–VIII*c* showed peaks in the region of 3400–3250 cm^{-1}, indicative of NH, and peaks at 1650–1640, 1550–1540, and 1290–1280 cm^{-1}, indicative of amide I, II, and III bands, respectively. IR spectra of X*a*–X*f* revealed a peak at around 1650 cm^{-1}, indicative of a tertiary amide carbonyl group.

For VIII*a*, the PMR spectrum ($CDCl_3$) exhibited peaks at δ 1.86 (s, 3H, methyl), 3.06 (d, 2H, methylene, J = 7 Hz), 5.15 (t, 1H, CH, J = 7 Hz), 5.80 (b, 1H, NH), and 7.25 (m, 14H, aromatic) ppm; mass spectrum: *m/e* (relative intensity) 315 (M^+, 2%), 314 (4), 272 (13), 258 (5), 224 (59), 182 (100), 181 (70), 180 (88), and 153 (59).

Hydrochloride Salts of *N*-Alkyl- and *N,N*-Dialkyl-1-(4-biphenylyl)-2-phenylethylamines—*Method G (VII, IX*a, *IX*b, *XI*a, *XI*b, *XI*c, *and XI*d)—To a magnetically stirred mixture of lithium aluminum hydride (0.05 mole) and absolute ether (300 ml) was added the appropriate *N*-acyl (V, VIII*a*, and VIII*b*) or *N*-acyl-*N*-alkyl (X*a*, X*b*, X*c* or X*e*, and X*d*, respectively) derivative (0.01 mole) under strictly anhydrous conditions. The reaction mixture was refluxed for 24 hr and cooled in an ice bath, and the excess hydride was decomposed by the dropwise addition of 4% NaOH.

The ethereal layer was separated, and the base was extracted with 10% HCl (50 ml). The acid extract was made alkaline with drops of concentrated ammonium hydroxide solution, and the liberated base was dissolved in ether. The ethereal layer was then washed several times with distilled water until free from alkalinity, dried over anhydrous sodium sulfate, and filtered. The hydrochloride salt was obtained by passing dry hydrogen chloride gas through the solution. The product was then recrystallized.

*Method H (XI*d *and XI*e)—A mixture of the appropriate amine hydrochloride (IX*b* and VI, respectively) (0.01 mole), formic acid (98%) (0.05 mole), and formaldehyde solution (38%) (0.022 mole) was refluxed for 12 hr. The reaction mixture was transferred to an evaporating dish and heated on a water bath until most of the unreacted formaldehyde and formic acid were removed. The syrupy residue was treated with formic acid (98%) (0.6 ml) and formaldehyde solution (38%) (0.2 ml) and allowed to evaporate on the water bath until dry. The last traces of water were azeotroped with absolute ethanol and benzene. The hydrochloride salt was prepared in the usual manner and then recrystallized.

IR spectra of VII and IX*a* showed broad peaks centered at the region of 2960–2700 cm^{-1}, indicative of NH_2^+. IR spectra of XII*a*–XI*e* revealed broad peaks centered at the region of 2650–2550 cm^{-1}, indicative of NH^+.

The PMR spectrum of VII ($CDCl_3$) exhibited peaks at δ 2.50 (s, 3H, methyl), 3.27 (d, 2H, methylene), 3.90 (m, 1H, CH), 6.90 (s, 5H, aromatic), 7.40 (m, 9H, aromatic), and 9.20 (b, 2H, NH_2^+) ppm.

Table III—Comparative Study of the Effects of Similar Molar Concentrations[a] of Some Tested Compounds with Papaverine

Compound	Mean Reduction[b] of Response[c], % ± *SE*
I	57.67 ± 1.36
XI*b*	64.00 ± 1.30
XI*d*	30.00 ± 1.18
XI*e*	68.00 ± 1.51

[a] The concentration used was 3×10^{-5} mole/ml. Aqueous solutions were used. [b] Average of three experiments. [c] Concentration produced by acetylcholine (0.2 μg/ml).

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Light-Scattering Studies on Bile Acid Salts II: Pattern of Self-Association of Sodium Deoxycholate, Sodium Taurodeoxycholate, and Sodium Glycodeoxycholate in Aqueous Electrolyte Solutions

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Abstract □ The pattern of self-association of the bile salts sodium deoxycholate, sodium glycodeoxycholate, and sodium taurodeoxycholate was investigated in aqueous electrolyte solutions by the light-scattering technique. The turbidity of the bile salt solutions was obtained over the concentration range of 0–20 mg/ml at 25°. These data were analyzed according to a monomer–micellar equilibrium model and a stepwise association model. Comparison of the light-scattering data with these models suggests that the monomer–micellar model may be inappropriate. Analysis of the data according to the stepwise association model suggests that the dihydroxy bile salts associate to form dimers, trimers, and tetramers in addition to a larger aggregate which varies in size depending on the degree of conjugation of the bile salt.

Keyphrases □ Bile salts, dihydroxy—self-association in aqueous electrolyte solutions, turbidimetric study □ Self-association—various dihydroxy bile salts in aqueous electrolyte solutions, turbidimetric study □ Turbidimetry—study of self-association of various dihydroxy bile salts in aqueous electrolyte solutions

The self-association of the dihydroxy bile salts has been studied extensively (1–5). Most often, the association pattern has been interpreted in terms of a monomer–micellar equilibrium model. This model is analogous to that utilized for flexible chain surfactants and involves the existence of a critical micelle concentration (CMC) below which surfactant aggregation is assumed to be negligible (6). Above the CMC, it is assumed that nearly all added surfactant in excess of the CMC associates to form micelles. Appreciable concentrations of intermediate-sized aggregates are presumed absent, and the polydispersity of the micelles is assumed to be small (7).

Previously (8), it was noted that the conditions necessary for the highly cooperative transition observed for flexible chain surfactants may not be met by all molecular structures. For example, rigid, planar aromatic structures such as dyes and purine and pyrimidine bases seem to associate by continuous stepwise self-association in which small aggregates such as dimers, trimers, and tetramers dominate (8). Furthermore, nonrigid aromatic structures such as the antihistamines self-associate in aqueous solution. Attwood and Udeala (9–11) showed that either pattern of association may dominate depending on the specific molecular structure.

The bile salts possess rigid but nonplanar molecular structures. However, unlike the dyes and the purine and pyrimidine bases, which are approximately symmetrical with respect to hydrophobicity on both sides of the ring, the bile salts consist of a rigid, nonplanar, alicyclic ring system in which one face is hydrophobic while the remaining face is hydrophilic because of the presence of either two or three hydroxyl groups. It was argued previously (12) that the association pattern of trihydroxy bile salts is best represented by a model that assumes the existence of some small aggregates such as dimers and trimers in addition to a higher aggregate.

The present paper extends previous work on the self-association of the bile salts to the dihydroxy bile salts including sodium deoxycholate, sodium taurodeoxycholate, and sodium glycodeoxycholate. The variation of the light scattered as a function of bile salt concentration was obtained in 0.15 *M* sodium halides. These data were analyzed in terms of a monomer–micellar equilibrium model and a stepwise association model in which it is assumed that appreciable concentrations of small multimers coexist with large aggregates.

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