2-(3-Biphenylyl)ethylamines: Potential Cardiovascular Agents

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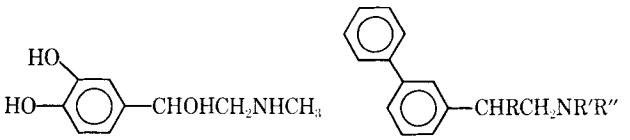
Abstract □ The preparation of a number of substituted 2-(3-biphenylyl)ethylamines is described. Blood pressure and nictitating membrane responses similar to β-phenylethylamine were noted in several compounds.

Keyphrases □ 2-(3-Biphenylyl)ethylamines—synthesis □ IR spectrophotometry—structure □ NMR spectroscopy—structure □ Pharmacological screening—2-(3-biphenylyl)ethylamines

The progress in the field of adrenergic drugs started with the elucidation of the structure of epinephrine (I) (1) and its synthesis (2, 3). Intensive pharmacological investigations thereafter were conducted and a great number of related amines were prepared and tested in an effort to correlate chemical structure to biological activity (4–6). The delineation of the biological properties of epinephrine and norepinephrine, the discovery of the advantageous adrenergic properties of ephedrine, and the proposal of the theory of α- and β-adrenergic receptors provided an impetus for the preparation of more specific adrenergic agents such as the CNS stimulants (6), bronchodilators (6), antiallergenic agents (7), nasal decongestants (7), anorexiants (8), α-blockers (9, 10), and β-blockers (10, 11).

Recently Cantarelli *et al.* (12) synthesized some biphenyl analogs of phenylethylamines and recorded their hypotensive and vasodilator effects. In a previous report (13) were described some derivatives of 2-(4-biphenylyl)ethylamines as possible cardiovascular and CNS agents. The present investigation deals with the preparation of a series of substituted 2-(3-biphenylyl)-ethylamines (II, Table I) for study in the treatment of cardiovascular diseases.



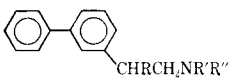
I II

The synthetic routes followed are outlined in Schemes I and II. The preparation of 3-acetylbiphenyl (III) was accomplished through the diazotization of 3-aminoacetophenone and then coupling with benzene. Rearrangement of III with sulfur and morpholine gave the *N*-biphenylylthioacetylmorpholine (IV) which upon hydrolysis with sodium hydroxide provided 2-(3-biphenylyl)acetic acid (V). Fusion of V with thiourea gave 2-(3-biphenylyl)acetamide (VI) which on reduction with lithium aluminum hydride yielded the 2-(3-biphenylyl)ethylamine (VII).

Conversion of VII to the guanidine derivative (VIII) was accomplished by fusion of the hydrochloride with cyanamide. The latter reaction gave, in addition to the guanidine derivative, a small amount of *N,N'*-bis[2-(3-biphenylyl)ethyl]urea (XVI). The latter also was prepared from the amine hydrochloride (VII) and urea.

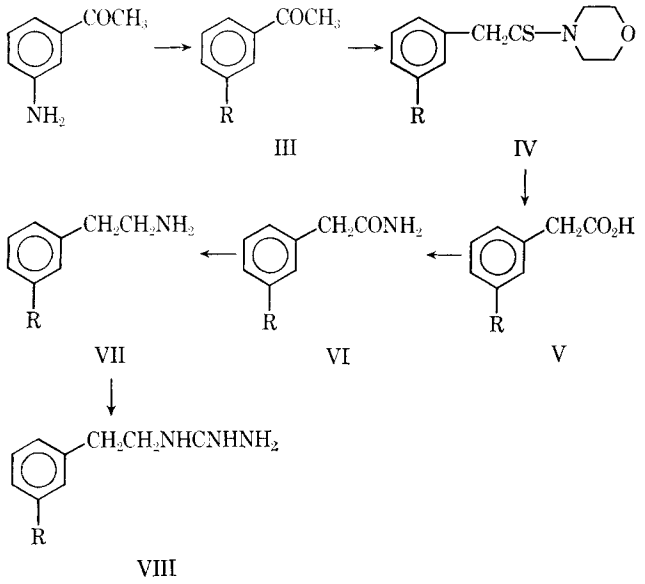
The bromination of III provided the bromoacetylbiphenyl (IX). The reduction of IX with sodium borohydride gave the corresponding bromoalcohol (X) which was utilized in the preparation of the *N*-substituted biphenylhydroxyethylamines (XI).

Table I—2-(3-Biphenylyl)ethylamines



No.	R	NR′R″	Method	Yield, %	M.p. °C. (Recrystn. Solvent)[a]	Molecular Formula	Anal., % Calcd. C	H	Cl	N	Found C	H	Cl	N
VII	H	NH_2	E	82	226–228 (ME)	$C_{14}H_{16}ClN$[b]	71.9	6.9	15.1	6.0	71.6	7.0	15.1	5.7
VIII	H	$NHCNHNH_2$	G	77	139–141 (ME)	$C_{15}H_{18}ClN_3$[b]	65.3	6.6	12.9	15.2	65.5	6.5	12.8	15.1
XI*a*	OH	$NHCH_3$	I[c]	53	144–146(ME)	$C_{15}H_{18}ClNO$[b]	68.3	6.9	13.4	5.3	67.9	7.0	13.6	5.1
XI*b*	OH	$NH(CH_2)_2CH_3$	I	43	159–161 (ME)	$C_{17}H_{22}ClNO$[b]	70.0	7.6	12.2	4.8	70.1	8.1	11.8	4.6
XI*c*	OH	$NHCH(CH_3)_2$	I	30	200–202 (E)	$C_{17}H_{22}ClNO$[b]	70.0	7.6	12.2	4.8	70.1	7.7	12.4	4.7
XI*d*	OH	$NH(CH_2)_3CH_3$	I	46	163–164 (ME)	$C_{18}H_{24}ClNO$[b]	70.7	7.9	11.6	4.6	70.9	8.0	11.7	4.4
XI*e*	OH	$NHC(CH_3)_3$	I	42	205–207 (E)	$C_{40}H_{52}N_2O_8 \cdot H_2O$[d]	68.0	7.7		4.0	68.2	7.6		3.7
XI*f*	OH	$NHCH_2C_6H_5$	I	25	193–195 (ME)	$C_{21}H_{22}ClNO$[b]	74.2	6.5	10.4	4.1	74.0	6.5	10.3	4.3
XI*g*	OH	$NH(CH_2)_2C_6H_5$	I	25	169–171 (ME)	$C_{22}H_{24}ClNO$[b]	74.7	6.8	10.0	4.0	74.7	6.7	9.9	4.0
XI*h*	OH	$NH(CH_2)_2C_6H_3$-(3,4-diCH_3O)	I	48	149–151 (ME)	$C_{24}H_{28}ClNO_3$[b]	69.6	6.8	8.63	3.4	69.1	6.8	8.8	3.2
XI*i*	OH	NHC_6H_{11}	I	25	217–219 (ME)	$C_{20}H_{26}ClNO$[b]	72.4	7.9	10.7	4.2	72.5	7.7	10.6	4.1
XI*j*	OH	NC_4H_8[e]	I	40	165–166 (ME)	$C_{18}H_{22}ClNO$[b]	71.2	7.3	11.7	4.6	71.4	7.7	11.7	4.5
XI*k*	OH	NC_5H_{10}[f]	I	24	224–226 (ME)	$C_{19}H_{24}ClNO$[b]	71.8	7.6	11.2	4.4	72.1	7.7	10.9	4.1
XI*l*	OH	NC_6H_{12}[g]	I	33	176–178 (ME)	$C_{20}H_{26}ClNO$[b]	72.4	7.9		4.2	72.1	8.0		4.3
XI*m*	OH	NC_4H_8O[h]	I	35	204–206 (ME)	$C_{18}H_{22}ClNO_2$[b]	67.6	6.9	11.1	4.4	67.6	6.8	11.1	4.5
XIII	OH	$N(CO)_2C_6H_4$[i]	K	65	134–136 (BH)	$C_{22}H_{17}NO_3$	76.8	5.0	4.1		77.2	5.3		4.4
XIV	OH	NH_2	L	76	223–225 (E)	$C_{14}H_{16}ClNO$[b]	67.3	6.5	14.2	5.6	67.3	6.6	14.1	5.8
XV	H	$NHCOCH_3$	F	62	96–97 (Et)	$C_{16}H_{17}NO$	80.3	7.2		5.9	80.4	7.2		6.0
XVI	H	$NHCONH(CH_2)_2C_{12}H_9$[j]	G, H	7, 84	193–194 (M)	$C_{29}H_{28}N_2O$	82.8	6.7		6.7	82.8	6.7		6.6

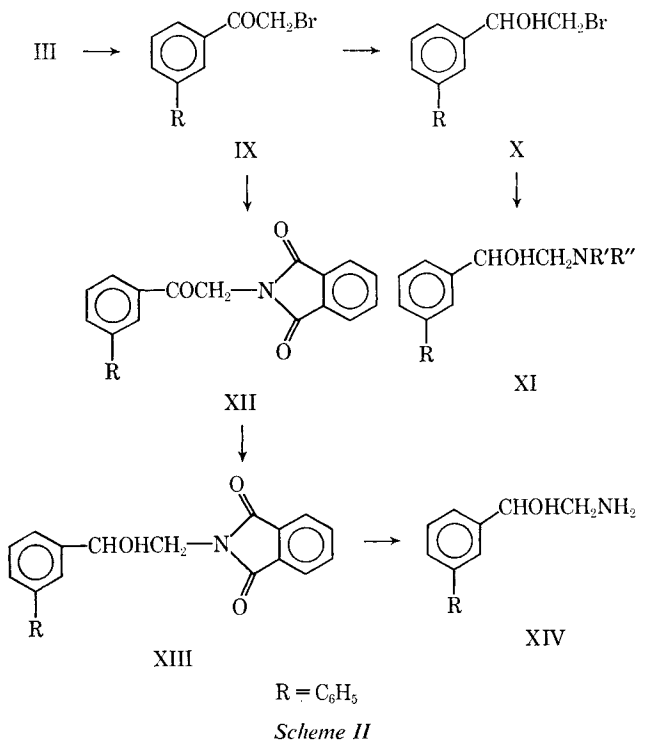
[a] ME = methanol–ether; E = ethanol; BH = benzene–n-hexane; Et = ether; M = methanol. [b] Hydrochloride. [c] Methylamine was used as 40% aqueous solution. [d] Tartrate. [e] Pyrrolidino. [f] Piperidino. [g] Homopiperidino. [h] Morpholino. [i] Phthalimido. [j] $C_{12}H_9$ = 3-biphenylyl.



Scheme I

Treatment of IX with potassium phthalimide gave the phthalimidoketone (XII) which upon reduction with sodium borohydride yielded the phthalimidoalcohol (XIII). Hydrolysis of the latter with hydrazine hydrate resulted in the formation of the biphenylylhydroxyethylamine (XIV). IR spectral data of the compounds reported in this study are summarized in Table II.

The compounds described in this study were tested for blood pressure and nictitating membrane responses. Compound XI*a* produced a blood pressure response equivalent to β-phenethylamine, whereas XIV produced only one-half the response. The other compounds were only weakly active. In terms of effects on the nictitating membrane, XI*a* was equivalent to β-phenylethylamine, whereas both VII and XIV were approximately twice as potent.



Scheme II

Table II—IR Spectral Data[a]

No.	Characteristic Bands, cm.$^{-1}$
III	3050 (CH_3); 1675 (C=O).
IV[b]	2930, 2830 (CH_2); 1670 (C=S); 1110 (CH_2—O—CH_2).
V	3050[c] (OH); 2900 (CH_2); 1700 (C=O).
VI	3400, 3200 (NH); 3030 (CH_2); 1660 (amide I), 1620 (amide II).
VII	2950 (CH_2); 1950[c] (NH_3^+).
VIII	3300, 3100 (NH); 2950 (CH_2); 1650 (C=N).
IX	2990, 2890 (CH_2); 1670 (C=O).
X[b]	3350 (OH); 2900 (CH_2).
XI*a*	3300 (OH); 2900 (CH_2); 2750 (NH_2^+).
XI*b*	3200 (OH); 2950 (CH_2); 2775 (NH_2^+).
XI*c*	3300 (OH); 2940 (CH_2); 2750 (NH_2^+).
XI*d*	3320 (OH); 2940 (CH_2); 2770 (NH_2^+).
XI*e*	3270 (OH); 2950 (CH_2); 2760 (NH_2^+).
XI*f*	3150 (OH); 2800 (CH_2); 2760 (NH_2^+).
XI*g*	3500 (OH); 2925 (CH_2); 2770 (NH_2^+).
XI*h*	3325 (OH); 2925 (CH_2); 2780 (NH_2^+); 1240, 1140 (C_6H_5-O-CH_3)
XI*i*	3300 (OH); 2900 (CH_2); 2770 (NH_2^+).
XI*j*	3225 (OH); 2900 (CH_2); 2670[c] (NH^+).
XI*k*	3250 (OH); 2900 (CH_2); 2700[c] (NH^+).
XI*l*	3275 (OH); 2900 (CH_2); 2700[c] (NH^+).
XI*m*	3220 (OH); 2960, 2850 (CH_2); 2650[c] (NH^+); 1135 (CH_2—O—CH_2).
XII	2900 (CH_2); 1775, 1730, 1695 (C=O).
XIII	3200 (OH); 2820 (CH_2); 1660 (C=O).
XIV	3300 (OH); 2950, 2850 (CH_2); 1960[c] (NH_3^+).
XV	3270 (NH); 2950 (CH_2); 1640 (amide I), 1550 (amide II).
XVI	3325 (NH); 2915, 2850 (CH_2); 1650 (amide I), 1570 (amide II).

[a] The compounds exhibited characteristic aromatic absorption bands in regions of 1600–1490 and 1000–695. [b] Liquid film (crude). [c] Broad.

EXPERIMENTAL[1]

3-Acetylbiphenyl (III)—*Method A*—The procedure employed was adapted from that described by Gomberg and Bachmann (14) for the preparation of 4-bromobiphenyl. To a suspension of 33.8 g. (0.25 mole) of 3-aminoacetophenone in 20 ml. of water was added 50 ml. of concentrated hydrochloric acid. The mixture was heated on a steam bath until solution occurred. Thereafter the solution was cooled gradually to 0–5° while stirring and then treated dropwise with a cooled solution of 18 g. (0.26 mole) of sodium nitrite in 35 ml. of water. The resulting stirred mixture was treated first with 300 ml. of benzene and thereafter with 58 ml. of a 5 *N* sodium hydroxide solution in drops over a period of 30–45 min. during which time the temperature was kept at about 5°. The temperature then was allowed to rise gradually to room temperature. The benzene layer was separated, washed several times with water until free of alkalinity, dried over anhydrous sodium sulfate, and thereafter concentrated under reduced pressure. The reddish brown oily residue was then distilled at 128–130°/0.2 mm. to give 29 g. (20%) of product. The 2,4-dinitrophenylhydrazone derivative was prepared in the usual manner and recrystallized from dilute methanol; m.p. 190–192° (lit. (15) m.p. 191–192°).

Method B—A method similar to that described by Cadogan (16) for aromatic arylation was followed. To a solution of 30 g. (0.222 mole) of 3-aminoacetophenone in 800 ml. of benzene was added 38 g. (0.324 mole) of isoamyl nitrite. The resulting solution was refluxed on a steam bath for 1 hr. and the reaction was then allowed to proceed at room temperature for 15 hr. The excess benzene was

[1] All melting points were taken in open glass capillaries using a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were determined on a Perkin-Elmer model 137 infracord spectrophotometer using potassium bromide pellets unless otherwise specified. NMR spectra were determined on a Varian A-60A spectrometer using tetramethylsilane as an internal standard; chemical shifts are recorded as δ values.

removed under reduced pressure and the reddish brown oily residue was then distilled at 128–130°/0.2 mm. to give 22.2 g. (51%) of 3-acetylbiphenyl (III).

N-(3-Biphenylylthioacetyl)Morpholine (IV)—Utilizing a method similar to that described by Sam *et al.* (13), a mixture of 29.4 g. (0.15 mole) of 3-acetylbiphenyl (III), 7.8 g. (0.24 mole) of sulfur, and 45 ml. of morpholine was refluxed on a steam bath for 8 hr. The product was dissolved in ether and washed several times with water till free of alkalinity. The ether layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residual reddish brown oil (46 g., 98%) was hydrolyzed without further purification.

2-(3-Biphenylyl)Acetic Acid (V)—*Method C*—To a solution of 21.2 g. (0.1 mole) of *N*-(3-biphenylylthioacetyl)morpholine (IV) in 100 ml. of ethanol was added a solution of 14.2 g. sodium hydroxide in 35 ml. of water. The resulting mixture was refluxed on a steam bath for 10 hr. and thereafter the ethanol was distilled under reduced pressure. The residual material was diluted with 400 ml. of water and acidified to pH 2 with concentrated hydrochloric acid. The solid was removed by filtration, washed several times with water, and recrystallized from benzene to yield 17.8 g. (84%) product, m.p. 135–136°.

Anal.—Calcd. for $C_{14}H_{12}O_2$: C, 79.2; H, 5.7. Found: C, 79.5; H, 5.9.

The NMR spectrum determined in deuterated acetone showed a singlet at 3.7, a broad peak at 6.4–6.9 (exchanged with D_2O), and a multiplet centered 7.5. The peaks are in the ratio of 2:1:9 and represent CH_2, OH, and aromatic H, respectively.

2-(3-Biphenylyl)Acetamide (VI)—*Method D*—A finely ground mixture of 16.1 g. (0.075 mole) of 2-(3-biphenylyl)acetic acid (V) and 6 g. (0.079 mole) of thiourea was heated gradually to 200–210° and maintained at this temperature for 1 hr. (13). The dark brown reaction mixture was cooled and triturated with 100 ml. of a 5% sodium hydroxide solution. The solid was removed by filtration, washed several times with water, and then recrystallized from benzene to give 11.7 g. (74%) of product, m.p. 154–155°.

Anal.—Calcd. for $C_{14}H_{13}NO$: C, 79.6; H, 6.2; N, 6.6. Found: C, 79.5; H, 6.2; N, 6.6.

The NMR spectrum determined in deuterated acetone showed a singlet at 2.8 (exchanged with D_2O), a singlet at 3.7, and a multiplet centered 7.5. The peaks are in the ratio of 2:2:9 and represent NH_2, CH_2, and aromatic H, respectively.

2-(3-Biphenylyl)Ethylamine Hydrochloride (VII)—*Method E*—A modification of the procedure described by Uffer and Schlittler (17) for the preparation of 2-phenylethylamine from 2-phenylacetamide was utilized. To a mixture of 7 g. of lithium aluminum hydride and 1.5 l. of dry ether was added 10.6 g. (0.005 mole) of 2-(3-biphenylyl)acetamide (VI). The stirred reaction mixture was refluxed for 20 hr. and then cooled in an ice bath. The excess hydride was decomposed by the dropwise addition of dilute sodium hydroxide solution. The ether layer was then separated, washed several times with water until free of alkalinity, and dried over anhydrous sodium sulfate. The amine was isolated as its hydrochloride and recrystallized.

N-[2-(3-Biphenylyl)Ethyl]Acetamide (XV)—*Method F*—Two grams (0.01 mole) of 2-(3-biphenylyl)ethylamine was heated on a steam bath with a mixture of 1.2 ml. of acetic anhydride and 0.5 g. of anhydrous sodium acetate. The reaction mixture was diluted with water and the product extracted with ether. The ether layer was washed with water, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The oily residue that solidified on cooling was recrystallized.

The NMR spectrum determined in deuterated chloroform showed a singlet at 1.9, a triplet centered 2.9, a quartet centered 3.6, a broad peak at 5.7–6.1 (exchanged with D_2O), and a multiplet centered at 7.5. The peaks are in the ratio 3:2:2:1:9 and represent CH_3, CH_2, CH_2, NH, and aromatic H, respectively.

[2-(3-Biphenylyl)Ethyl]Guanidine Hydrochloride (VIII)—*Method G*—The method used was adapted from that described by Short and Darby (18) for the preparation of guanidines. A mixture of 1.2 g. (0.005 mole) of 2-(3-biphenylyl)ethylamine hydrochloride (VII), 0.25 g. (0.006 mole) of cyanamide and 3 ml. of water was heated in an oil bath at 180° for 3.5 hr. The cooled reaction mixture was triturated with hot methanol, and then cooled. The solid that separated was removed by filtration and identified as XVI (see *Method H*). The guanidine derivative was precipitated from the filtrate by the addition of dry ether and then recrystallized.

N,N-Bis[2-(3-Biphenylyl)Ethyl]Urea (XVI)—*Method H*—A method similar to that described by Davis and Blanchard (19) for the preparation of symmetrically disubstituted ureas was utilized. A mixture of 0.5 g. (0.002 mole) of 2-(3-biphenylyl)ethylamine hydrochloride (VII), 0.062 g. (0.001 mole) of urea, and 1.5 ml. of water was heated in an oil bath to 200° for 3.5 hr. The reaction mixture was cooled and then recrystallized.

The NMR spectrum determined in deuterated dimethylsulfoxide showed a triplet centered 2.8, a multiplet centered 3.3, a broad peak at 5.6–6.1 (exchanged with D_2O), and a multiplet centered at 7.5. The peaks are in the ratio of 2:2:1:9 and represent CH_2, CH_2, NH, and aromatic H, respectively.

α-Bromomethyl-3-biphenylylcarbinol (X)—A method similar to that reported by Sam *et al.* (13) for the preparation of α-chloromethyl-4-biphenylylcarbinol was followed. A cooled, stirred solution of 13.8 g. (0.05 mole) of 3-phenylphenacyl bromide (IX), prepared according to the method of Cavallini *et al.* (20), in 500 ml. of ethanol was treated in divided portions with 9 g. of sodium borohydride. The mixture was stirred at room temperature for 18 hr. and the solvent was then removed under reduced pressure. The residue was treated with 10% hydrochloric acid and exhaustively extracted with chloroform. The extract was washed with water, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residual yellowish brown oil (90%) was used without further purification for the condensation with amines in *Method I*.

α-Alkylaminomethyl-3-biphenylylcarbinols (XI)—*Method I*—To a solution of 0.01 mole of α-bromomethyl-3-biphenylcarbinol (X) in 50 ml. of ethanol was added dropwise a solution containing 0.6 g. of sodium hydroxide, 4 ml. of water, 25 ml. of ethanol, and 0.3 mole of the appropriate amine. The reaction mixture was stirred at room temperature for 20 hr. The solvent was distilled under reduced pressure and the residue treated with water and exhaustively extracted with ether. The ether extract was washed several times with water until free of alkalinity and dried over anhydrous sodium sulfate. The amine was converted to a salt in the usual manner and recrystallized.

N-(3-Phenylphenacyl)Phthalimide (XII)—*Method J*—The procedure employed was essentially the same as that described by Sam *et al.* (13) for the preparation of *N*-(4-phenylphenacyl) phthalimide. A solution of 21 g. (0.076 mole) of 3-phenylphenacyl bromide (IX) (20) in 200 ml. of *N,N*-dimethylformamide was treated with 15.3 g. (0.084 mole) of potassium phthalimide. The stirred mixture, after remaining at room temperature for 15 hr., was treated with 300 ml. of water and then extracted with chloroform. The chloroform extract was washed with dilute alkali and water, respectively, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The reddish brown oily residue which solidified on cooling was washed with ether and recrystallized from dioxane-water to give 8.3 g. (32%) of product, m.p. 159–160°

Anal.—Calcd. for $C_{22}H_{15}NO_3$: C, 77.4; H, 4.4; N, 4.1. Found: C, 76.9; H, 4.6: N, 4.3.

The NMR spectrum determined in deuterated chloroform showed a singlet at 5.1 and a multiplet centered at 7.7. The peaks are in the ratio of 2:13 and represent CH_2 and aromatic H, respectively.

N-[2-Hydroxy-2-(3-Biphenylyl)Ethyl]Phthalimide (XIII)—*Method K*—The procedure employed was a modification of that described for the preparation of X. To a solution of 10 g. (0.03 mole) of *N*-(3-phenylphenacyl)phthalimide (XII) in 250 ml. of dioxane was added alternately and in divided portions 5 g. of sodium borohydride and 250 ml. of ethanol. The reaction mixture was then processed as in the case of X. The residue obtained after the removal of the chloroform was recrystallized.

2-Hydroxy-2-(3-Biphenylyl)Ethylamine Hydrochloride (XIV)—*Method L*—The method described by Sam *et al.* (13) for the preparation of 2-hydroxy-2-(4-biphenylyl)ethylamine was modified slightly and followed. A solution of 5 g. (0.015 mole) of *N*-[2-hydroxy-2-(3-biphenylyl)ethyl]phthalimide (XIII) in 100 ml. of ethanol was treated with 10 ml. of hydrazine hydrate (99–100%). The reaction mixture was refluxed for 96 hr. The solvent was removed under reduced pressure; the residue was stirred for 2 hr. and treated with a mixture of 25 ml. of 2 *N* ammonia, 30 ml. of water, and 35 ml. of chloroform. The chloroform layer was separated and extracted with four portions of 75 ml. of *N* acetic acid. The acetic acid solution was treated with excess ammonia and then exhaustively extracted with ether. The ether extract was washed several times with water until free of alkalinity and then dried over

anhydrous sodium sulfate. The amine was converted in the usual manner to the hydrochloride and recrystallized.

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Cholecystokinin-Like Activities in Guinea Pigs and in Dogs of the C-Terminal Octapeptide (SQ 19,844) of Cholecystokinin

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Abstract □ The synthetic C-terminal octapeptide of cholecystokinin (CCK), SQ 19,844, caused CCK-like contractile activities of excised gallbladder and ileal strips of guinea pigs, of gallbladder preparations *in situ* in anesthetized guinea pigs, and of gallbladder and duodenal preparations *in situ* in anesthetized dogs. In these preparations, SQ 19,844 was about 10 and 2.5 times more potent than CCK on a weight basis and molar basis, respectively. The duration of the effect of SQ 19,844 on the gallbladder was about one-half that of CCK. In fasted unanesthetized dogs with gastric pouches, the secretory stimulant potency of SQ 19,844 was only about four-fifths and one-third that of CCK on a weight basis, and molar basis, respectively. The C-terminal tetrapeptide, which was more potent than either SQ 19,844 or CCK as a gastric secretory stimulant, was considerably less potent in contracting the gallbladder.

Keyphrases □ Cholecystokinin—gallbladder-intestinal contraction, gastric secretion □ C-terminal octapeptide—gallbladder-intestinal contraction, gastric secretion □ Gallbladder contraction—C-terminal tetrapeptide, protected □ C-terminal tetrapeptide, protected—gastric secretion □ Peptides, cholecystokinin related—gallbladder-intestinal contraction, gastric secretion

In 1928, Ivy and Oldberg reported (1) that an extract of the upper intestinal mucosa promoted contraction and evacuation of the gallbladder. This extract contained a substance that they named cholecystokinin, herein designated as CCK. CCK is a single-chain polypeptide with 33 aminoacid residues (2). The C-terminal pentapeptide of CCK is identical (3) with that of gastrin (4, 5). Harper and Raper in 1943 (6) and Crick *et al.* in 1949 (7) demonstrated that the mucosa of the upper intestine contained a substance that promoted pancreatic secretion of enzymes; they named this substance pancreozymin. Mutt and Jorpes (8, 9) have found that CCK activity and pancreozymin activity accompanied each other during purification; accordingly, CCK and pancreozymin may be identical (8–10). Mutt and Jorpes (8–10) reported that pure CCK, tested on the guinea pig gallbladder, assays at 3,000 Ivy dog units/mg.

A partial determination of the aminoacid sequence of CCK was reported recently by Mutt and Jorpes (10–12), who also isolated the C-terminal octapeptide of CCK after tryptic digestion (9–12) and noted that it was very active in contracting the gallbladder and in promoting secretion of pancreatic enzymes. This octapeptide was synthesized by Ondetti *et al.* (13) at the Squibb Institute and is referred to as SQ 19,844. The sequence of aminoacid residues in CCK and in SQ 19,844 is as follows:

$$\text{Lys}\cdot(\text{Ala}_1, \text{Gly}_1, \text{Pro}_1, \text{Ser}_1)\cdot\text{Arg}\cdot\text{Val}\cdot(\text{Ileu}_1, \text{Met}_1, \text{Ser}_1)\cdot\text{Lys}\cdot$$
$$\text{Asn}\cdot(\text{Asx}_1, \text{Glx}_1, \text{His}_1, \text{Leu}_2, \text{Pro}_1, \text{Ser}_2)\cdot\text{Arg}\cdot\text{Ileu}\cdot(\text{Asp}_1, \text{Ser}_1)\cdot$$
$$\text{Arg}\cdot\text{Asp}\cdot\underset{\displaystyle\text{SO}_3\text{H}}{\text{Tyr}}\cdot\text{Met}\cdot\text{Gly}\cdot\text{Trp}\cdot\text{Met}\cdot\text{Asp}\cdot\text{Phe}\cdot\text{NH}_2$$

Cholecystokinin (CCK)

$$\underset{\displaystyle\text{SO}_3\text{H}}{\text{Asp}}\cdot\text{Tyr}\cdot\text{Met}\cdot\text{Gly}\cdot\text{Trp}\cdot\text{Met}\cdot\text{Asp}\cdot\text{Phe}\cdot\text{NH}_2$$

SQ 19,844