Synthesis of 1,2,3,4-Tetrahydroquinazoline Derivatives as Potential *alpha*-Adrenergic Blocking Agents

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The synthesis of *N,N'*-bis[6-(1,2,3,4-tetrahydro-3-quinazolidyl)hexyl]cystamine (I) and 3-(6-aminohexyl)-1,2,3,4-tetrahydroquinazoline (II) are described. Compound I is obtained by condensation of *o*-nitrobenzoyl chloride with 3-(6-aminohexyl)-1,3-thiazolidine (III) followed by dimerization, reduction and formation of tetrahydroquinazoline ring. A similar method was used for preparation of compound II. These compounds and some synthesis intermediates are potential *alpha*-adrenergic blockers.

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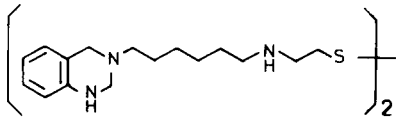
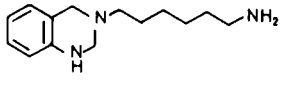
In recent years [1] a group of tetramine disulfides with irreversible blocking character associated with a high selectivity over the *alpha*-adrenoceptor has been reported. The studies of structure-activity relationships carried out with those substances led to two head-series with a maximum of activity, *N,N'*-bis(*o*-methoxybenzylamino-*n*-hexyl)-cystamine (BHC) and *N,N'*-bis-(5-aminopentyl)cystamine (AOC), which on the basis of their molecular features as well as to that of related compounds, allowed the postulation of a topographic model for the forenamed receptor [2]. With the goal to contribute to the knowledge of the *alpha*-adrenoceptor we are concerned with the chemical and subsequently the pharmacological description of related polyamine disulfides with potential irreversible *alpha*-blocking character and of its structural analogs lacking the cystamine group with reversible action.

In the present paper we report the synthesis of *N,N'*-bis[6-(1,2,3,4-tetrahydro-3-quinazolidyl)hexyl]cystamine (I) and 3-(6-aminohexyl)-1,2,3,4-tetrahydroquinazoline (II).



I



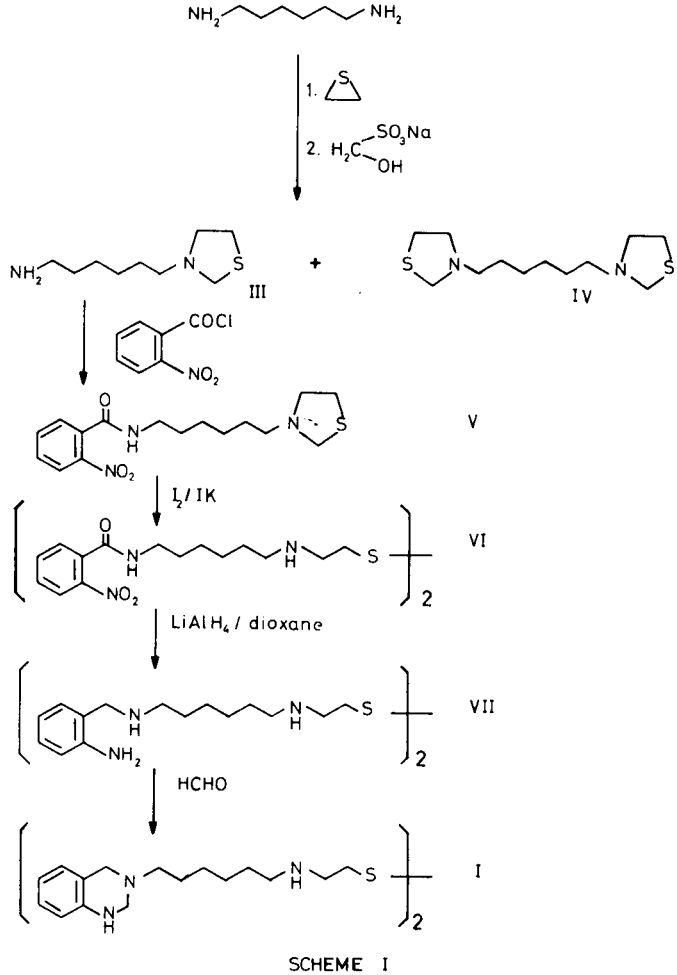
II

Both compounds have a high functionalization, specially three different types of amino groups, so their synthesis must be carried out from products with well differentiated functional groups.

The preparation of compound I, a symmetrical disulfide, can be achieved by dimerization of a previously formed structure or by simultaneous lengthening by the two ends of a short symmetric disulfide. In our case, the first approach was the most convenient.

Compounds I and II show an heterocyclic system of 3-alkyl substituted tetrahydroquinazoline as a fundamental structural feature. According to the literature this system is prepared by one of the three following general ways: a) reduction of quinazolones and quinazolinones [3]; b) Reduction of 3-alkylquinazolonium salts [4]; c) formation of the heterocyclic ring from a suitable *o*-aminobenzylamine [4a,5].

Upon consideration of the three approaches, we decided that the third would be the most satisfactory for the purpose which is the pathway shown in Scheme I.



SCHEME I

The 3-(6-aminohexyl)-1,3-thiazolidine (III) is the key intermediate for the development of the synthesis because it has the two amino groups separated by the six methylene groups of the final structure I; one is a primary amine and the other is protected in the form of the thiazolidine which is easily transformable into cystamine in only one step.

The thiazolidine III was prepared from 1,6-hexanediamine according to the Wineman method [6] which is mercaptoethylation of 1,6-hexanediamine and reaction of the aminothiol obtained with formaldehyde bisulfite. In this two-step process the *N,N'*-hexamethylene-di-1,3-thiazolidine IV, characterized by its spectroscopic data and elemental analysis was also isolated. The pmr spectrum of IV differs only from that of III in the absence of signals assignable to the interchangeable protons (addition of trifluoroacetic acid) and in the integral ratio of the signals attributed to a methylene of the heterocyclic ring with respect to the broad signal due to the four methylene groups of the central chain. Such an integral ratio confirms the presence of the two thiazolidine rings in the byproduct IV obtained.

Condensation of III with *o*-nitrobenzoyl chloride in anhydrous benzene and in the presence of triethylamine afforded the *N*-[6-(3-thiazolidyl)hexyl]-*o*-nitrobenzamide V in high yield. Its ir spectrum shows, as the more characteristic signals, an absorption at 1600 cm^{-1}, due to the carbonyl vibration of the amide group, and the asymmetric and symmetric stretching of the nitro group at 1520 and 1350 cm^{-1}. The pmr spectrum shows at δ 8.20 and 7.20 a complex signal corresponding to the protons of the ABCD system of the aromatic ring, a singlet at δ 3.96 of the methylene groups between heteroatoms in the thiazolidine ring and AA'BB' system of the other attached methylene groups of the same ring between δ 3.20-2.60.

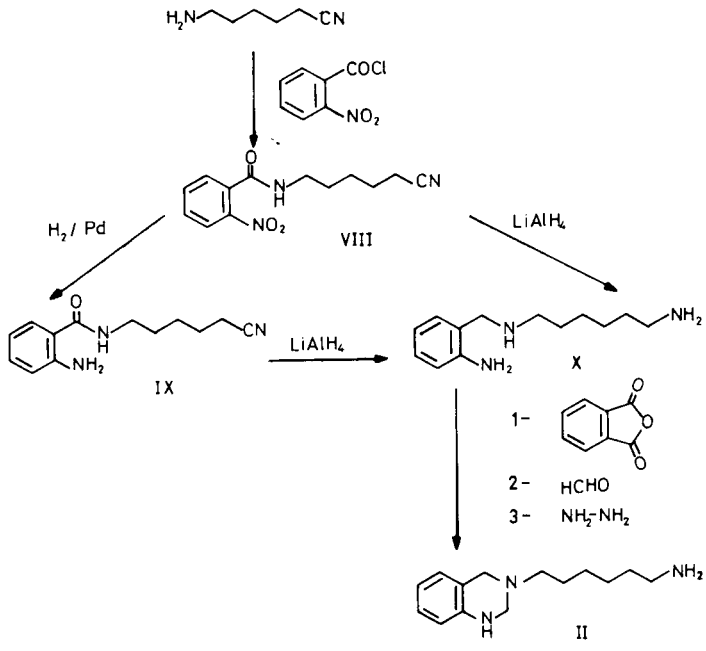
Dimerization of V by means of a 0.1 *N* solution of iodine stabilized with a 2.5% of potassium iodide afforded the *N,N'*-bis(*o*-nitrobenzoylaminohexyl)cystamine VI in 80% yield. Its spectrum differs from that of the compound V in the disappearance of the typical signals of the thiazolidine ring and in the appearance of a multiplet at δ 3.18-2.30 due to the ethylene groups between the heteroatoms.

The synthesis of I was accomplished by means of the reduction of the system of the *o*-nitrobenzamide of VI to a suitable *o*-aminobenzylamine to form the desired tetrahydroquinazoline by reaction with formaldehyde.

Reduction of VI to the *N,N'*-bis(*o*-aminobenzylaminohexyl)cystamine VII was carried out by means of an excess of lithium aluminium hydride in boiling dioxane for 5 hours. Previous experiments using diethyl ether or tetrahydrofuran as solvents were unsuccessful because of the very low solubility of VI in these solvents. The low temperatures attainable under those conditions forced us to increase considerably the reaction times with undesirable results which as the simultaneous reduction of the disulfide group to a thiol group and the partial decomposition of the product VII with the consequent lowering of the yield. Sodium borohydride with cobaltous chloride as catalyst [7] which allows the use of such solvents as methanol or dioxane, both of them better solvents of VI, were also tested as reducing agents. Since several assays with this last reagent under different conditions afforded mixtures of VI and VII with a considerable decrease of the total amount of substance. For the reduction of VI, refluxing mixtures of lithium aluminium hydride in anhydrous dioxane is the reagent of choice. The structure of VII is consistent with its spectroscopic data, especially with the disappearance in the ir spectrum of the characteristic signals of the carbonyl and nitro groups; the presence at δ 3.55 in the pmr spectrum corresponding to the benzylic methylene group and the base peak of the mass spectrum of m/e 106, due to the *o*-aminobenzyl ion. In the ms of that family of disulfides of high molecular weight we have not observed the molecular ion peak, but there are readily observable signals of m/e higher than M/2.

Compound VII, not previously synthesized, is an analog of BHC, differing only by the substitution of the methoxy group in the aromatic ring of the BHC by an amino group in VII. For this reason its pharmacological evaluation should be very interesting.

In the last step of the synthetic method, I was prepared by treatment of VII with aqueous-methanolic formaldehyde in basic medium by refluxing for thirty minutes. The pmr spectrum of the resulting product shows as the more characteristic signals, a singlet at δ 3.80 assigned to the



SCHEME II

methylene group between the nitrogen atoms of the tetrahydroquinazoline system.

The preparation of II was accomplished in a manner similar to that described for I.

In this case, the starting product was 6-aminohexanenitrile and the final primary amino group is introduced as a latent group by means of the nitrile function. The condensation of *o*-nitrobenzoyl chloride with 6-aminohexanenitrile affords VIII in 88% yield. Its ir spectrum shows absorptions at 2250 cm^{-1} nitrile stretching, 1660 cm^{-1} amide carbonyl group, and 1530 and 1350 cm^{-1} due to the nitro group. The pmr spectrum exhibits a multiplet at δ 8.03-7.66 assigned to the aromatic protons, a complex signal between δ 3.46-2.86 due to the methylene attached to the amide nitrogen atom, a triplet at δ 2.40 from the methylene contiguous to the nitrile group and another broad signal between δ 1.93 and 0.80 due to the three central methylene groups in the carbon chain.

Reduction of VIII was carried out by two alternative methods. The first was the simultaneous reduction of the three functional groups using lithium aluminium hydride suspended in refluxing anhydrous diethyl ether as the reducing agent. In this way, X was obtained in a 23% yield. Another and a more satisfactory method consists in the previous reduction of the nitro group in the usual catalytic manner and then later reduction of the other functional group with lithium aluminium hydride in dioxane. In this way, X was obtained in 89% overall yield (See Scheme II).

Spectroscopically, IX differs from VIII in the disappearance of the signals due to the nitro group in its ir spectrum and in the pmr spectrum a chemical shift to higher fields is observed in the aromatic region that appears as a multiplet at δ 6.29-7.52. The spectral characteristics of X are similar to those described for VII.

The last step of this Scheme is quite different from that of Scheme I. In this instance we have a primary aliphatic amine and it was necessary to protect it as demonstrated by the direct treatment of X with formaldehyde yielding amorphous polymeric substances only. The protection of that functional group was accomplished taking advantage of the different nucleophilicity of the primary aromatic and the aliphatic amines and the very distinct favorable sterical enhancement of these groups in the molecule.

Treatment of X with phthalic anhydride yields its 6-phthalimido derivative. The assignment of its structure was made on the basis of its mass spectrum in which apart from the molecular peak (m/e 351), a fragment of *o*-aminobenzyl (m/e 106) as well as the phthalimide *N*-alkyl substituted fragmentation products were also observed.

The reaction of the phthalimido derivative with formaldehyde under analogous conditions to the formation of I led to the tetrahydroquinazolidine system, confirmed by the appearance in its pmr spectrum of a singlet at δ 3.80 assigned to the new methylene group between the two nitrogen atoms, as well as the molecular peak in its ms.

Finally, elimination of the protecting group by hydrazinolysis leads to compound II in 15% of overall yield for the last three steps.

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R-14 B Spectrometer (60 Hz, tetramethylsilane at δ 0.0 (ppm) as internal standard) with deuteriochloroform as the solvent. Chemical shifts are reported as δ values and are in parts per million (ppm). Infrared spectra were determined on a Perkin-Elmer 577 Spectrophotometer. The mass spectrum was determined on an AEI (model MS-902 S) Mass Spectrometer. Elmental analyses were performed by Instituto de Química Bioorgánica, Barcelona.

3-(6-Aminohexyl)-1,3-thiazolidine (III).

A solution of 1,6-hexanediamine (150 g, 1.29 moles) in dry benzene (300 ml) contained in a flask provided fitted with a Dean-Stark trap was boiled for 1 hour under a nitrogen atmosphere. After cooling to 40-50° a solution of thiirane (9.69 g, 0.16 mole) in dry benzene (125 ml) was slowly added and the mixture refluxed for 2 hours. The solvent was removed and the oily residue was distilled under vacuum (96°, 22 mm Hg) in order to eliminate excess 1,6-hexanediamine. The non-volatile fraction, under these conditions, was dissolved in methanol (150 ml) and to this was added a solution of formaldehyde bisulfite (122 g, 0.98 mole) in water (125 ml). The mixture was stirred at reflux temperature for 12 hours. The

Table I

Compound	Mp °C (Solvent) [a]	Yield %	Formula	Analyses % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found	Chloride Calcd.	Chloride Found
III-HCl	87-90 (A)	53	$C_9H_{20}N_2S \cdot 2HCl$	41.37	41.06	8.45	8.45	10.72	10.55	12.27	12.43	27.14	26.94
IV	63-64 (E)	2.5	$C_{12}H_{24}N_2S_2$	60.35	60.14	10.68	10.22	8.76	8.62	20.16	19.92	—	—
V-HCl	173-175 (A)	99	$C_{16}H_{23}N_3O_3S \cdot HCl$	51.39	51.12	6.47	6.61	11.03	11.07	8.57	8.39	9.48	9.62
VI-HI	115.116 (F)	80	$C_{30}H_{42}N_6O_6S_2 \cdot 2HI$	39.91	39.58	5.13	5.07	9.31	9.09	7.09	7.10	—	—
VII-HCl	134-136 (F)	43	$C_{30}H_{52}N_6S_2 \cdot 6HCl$	46.54	46.75	7.81	7.85	10.18	9.89	7.76	7.42	25.76	25.83
I-Picrate	69-70 (F)	96	$C_{32}H_{52}N_6S_2 \cdot 6C_6H_3O_7N_3$	41.67	41.66	3.57	3.64	17.16	17.01	3.26	3.67	—	—
VIII	71-73 (A)	88	$C_{13}H_{15}N_3O_3$	59.75	59.68	5.78	5.78	16.08	15.77	—	—	—	—
X-Oxalate	103-105 (M)	89	$C_{13}H_{23}N_3 \cdot 3C_2H_2O_4$	46.43	46.81	5.94	6.16	8.55	8.30	—	—	—	—
II-Oxalate	115-118 (M)	15	$C_{14}H_{23}N_3 \cdot 3C_2H_2O_4$	47.71	47.72	5.80	5.81	8.34	8.19	—	—	—	—

[a] Solvents: A = acetonitrile, E = ether, F = ethanol, M = methanol.

methanol was removed and the aqueous layer extracted with ether and then with chloroform in a continuous liquid-liquid extractor for 3-4 days. The ethereal solution was dried over anhydrous magnesium sulfate and after evaporation under vacuum, a white solid was obtained which was identified as a *N,N'*-hexamethylene-di-1,3-thiazolidine IV (0.6 g, 2.5%), mp 63-64°; pmr: 4.00 (s, 2H, N-CH_2-S), 2.95 (AA'BB', 8H, N-CH_2-CH_2-S), 2.35 (t, 4H, CH_2-N), 1.90-1.15 (broad signal, 8H, $(CH_2)_4$). The chloroform solution was dried over anhydrous magnesium sulfate, the solvent removed and the residue distilled (150°, 0.3 mm Hg) to give the desired compound III (15.7 g, 53%) as a colourless oil; pmr: 4.00 (s, 2H, N-CH_2-S), 3.66-2.55 (m, 6H, H_2N-CH_2 and N-CH_2-CH_2-S), 2.36 (t, 2H, CH_2-N), 1.70-1.06 (broad signal, 8H $(CH_2)_4$), 1.80 (s, 2H, NH_2); ms: m/e (relative intensity) 189 (M + 1, 4), 155 (22), 112 (13), 110 (15), 102 (85), 98 (24), 88 (30), 84 (15), 70 (24), 58 (30), 56 (63), 44 (45), 42 (100), 41 (50).

N-[6-(3-Thiazolidyl)hexyl]-*o*-nitrobenzamide (V).

To a magnetically stirred solution of III (2 g, 10.6 mmoles) and triethylamine (2.7 g, 26 mmoles) in dry benzene (80 ml) was added dropwise a solution of *o*-nitrobenzoyl chloride (1.96 g, 10.6 mmoles) in anhydrous benzene. Agitation was continued for 5 hours at room temperature. After this time the solution was washed with water and extracted with hydrochloric acid. The aqueous layer was basified with 2*N* sodium hydroxide and extracted with benzene. The organic layer dried over anhydrous magnesium sulfate and evaporated to give V (3.63 g, 99%) as an oil; pmr: 8.20-7.20 (m, 4H, Ar-H), 6.60-6.20 (broad signal, 1H, NH-CO), 3.96 (s, 2H, N-CH_2-S), 3.60-3.15 (m, 2H, CH_2-NHCO), 3.20-2.60 (AA'BB', 4H, N-CH_2-CH_2-S), 2.31 (t, 2H, N-CH_2), 1.91-1.10 (broad signal, 8H, $(CH_2)_4$); ir (chloroform): 3445 cm^{-1} and 3310 cm^{-1} (st, NH), 1660 cm^{-1} (st, CO), 1520 cm^{-1} (st as, NO_2), 1350 (st si, NO_2), 675 cm^{-1} (st, C-S).

N,N'-bis[6-(*o*-Nitrobenzoylamino)hexyl]cystamine (VI).

An aqueous solution of iodine with a 2.5% potassium iodide (250.7 ml, 0.1 *N*) was slowly added to a solution of V (8.45 g, 25 mmoles) in ethanol (250 ml). The mixture was stirred for 12 hours at room temperature. After this time water was removed under vacuum, the solid residue treated with 2 *N* sodium hydroxide and extracted with chloroform. The chloroformic layer was dried over anhydrous magnesium sulfate and evaporated to give VI as a yellow oil (6.46 g, 80%); pmr: 8.20-7.10 (m, 8H, Ar-H), 6.90-6.51 (broad signal, 2H, NH-CO), 3.50-3.18 (m, 4H, CH_2-NHCO), 3.18-2.30 (m, 12H, CH_2-N, N-CH_2-CH_2-S), 1.89 (s, 2H, NH), 1.80-1.05 (broad signal, 16H, $(CH_2)_4$); ir (chloroform): 3290 cm^{-1} (st, NH), 1640 cm^{-1} (st, CO), 1530 cm^{-1} (st as, NO_2), 1350 cm^{-1} (st si, NO_2), 640 cm^{-1} (st, C-S).

N,N'-bis[6-(*o*-Aminobenzylamino)hexyl]cystamine (VII).

A solution of VI (4.39 g, 6 mmoles) in dry dioxane (150 ml) was slowly added to a suspension of lithium aluminium hydride (3.59 g, 90 mmoles) in dry dioxane (70 ml). The mixture was stirred at reflux temperature for 5 hours. A nitrogen atmosphere was maintained in a system during the entire process. The solution was cooled and water (3.6 ml), dioxane (3.6 ml), 2 *N* sodium hydroxide (7.6 ml) and water (10 ml) were added in the order indicated. The suspension which formed was filtered, the solid washed several times with chloroform and all the liquid fractions combined, dried over anhydrous magnesium sulfate and the solvent removed under vacuum to give VII as an oil (1.6 g, 43%), bp 200° 0.7 mm Hg; pmr: 7.25-6.25 (m, 8H, Ar-H), 3.55 (s, 4H, Ar-CH_2-NH), 3.05-1.90 (m, 24H, CH_2-N, N-CH_2-CH_2-S, NH), 1.90-0.90 (broad signal, 16 H, $(CH_2)_4$); ir (chloroform): 3400 cm^{-1} (st, NH), 660 cm^{-1} (st, C-S); ms: m/e (relative intensity): 323 (1), 308 (1), 277 (2), 122 (20), 120 (40), 119 (33), 118 (50), 112 (32), 108 (21), 107 (53), 106 (100), 105 (37), 104 (37), 98 (37), 92 (79), 79 (47), 65 (19).

N,N'-bis[6-(1,2,3,4-Tetrahydro-3-quinazolidyl)hexyl]cystamine (I).

To a solution of VII (2 g, 3 mmoles) and potassium hydroxide (0.23 g, 4 mmoles) in methanol (50 ml) was added an aqueous solution of 40% formaldehyde (0.91 g, 10 mmoles). The mixture was stirred at reflux temperature for 1 hour, the methanol was removed and to the resulting residue water was added. The aqueous layer was extracted with chloroform, the organic solvent dried over anhydrous meagnesium sulfate and evaporated to give I as an oil (2.04 g, 96%); pmr: 7.65-6.50 (m, 8H, Ar-H), 4.09 (s, 4H, N-CH_2-N), 3.75 (s, 4H, Ar-CH_2-N), 3.90-2.03 (m, 14H, N-CH_2-CH_2-S, CH_2-N, NH), 0.91-1.80 (broad signal, 16H, $(CH_2)_4$); ir (chloroform): 3400 cm^{-1} (st, NH), 660 cm^{-1} (st, C-S).

N-(5-Cyanopentyl)-*o*-nitrobenzamide (VIII).

To a solution of 6-aminohexanenitrile (11.98 g, 0.1 mole) and triethylamine (25.27 g, 0.25 mole) in dry benzene (450 ml) was added dropwise a solution of *o*-nitrobenzoyl chloride (18.4 g, 0.1 mole) in dry benzene (210 ml). The mixture was stirred for 5 hours at room temperature, washed with water, dried over anhydrous magnesium sulfate and evaporated to give VIII (23.71 g, 88%); pmr: 8.02-7.66 (m, 4H, Ar-H), 3.46-2.25 (m, 2H, CH_2-NHCO), 2.50 (t, 2H, CH_2-CN), 1.90-0.80 (broad signal, 6H, $(CH_2)_3$), ir (chloroform): 3240 cm^{-1} (st, NH), 2250 cm^{-1} (st, CN), 1660 cm^{-1} (st, CO), 1530 cm^{-1} (st as, NO_2), 1350 cm^{-1} (st si, NO_2).

N-(5-Cyanopentyl)-*o*-aminobenzamide (IX).

To a solution of VIII (10 g, 38 mmoles) in ethanol (300 ml) was added 10% paladium-charcoal (625 mg) and the mixture was hydrogenated at room temperature and atmospheric pressure for 24 hours. After this time another portion of the catalyst (625 mg) was added and the hydrogenation was prolonged until abosorption of hydrogen ceased. Filtration and evaporation of the solvent gave IX as a yellow solid (8.71 g, 98%); pmr: 7.52-6.29 (m, 4H, Ar-H), 6.52 (d, 2H, Ar-NH_2), 5.32 (broad signal, 1H, CONH), 3.25 (m, 2H, CONH-CH_2), 2.21 (t, 2H, CH_2CN), 1.50 (broad signal, 6H, $(CH_2)_3$); ir (chloroform): 3350-3450 cm^{-1} (st, NH), 2250 cm^{-1} (st, CN), 1630 cm^{-1} (st, CONH).

N-(*o*-Aminobenzyl)-1,6-hexanediamine (X).

Reduction of IX was carried out in a manner similar to that for VI. The molar ratio between IX and lithium aluminium hydride was 1:6. Compound X was obtained as a red oil (91%); pmr: 7.20-6.32 (m, 4H, Ar-H), 3.65 (s, 2H, Ar-CH_2-NH), 2.75-2.32 (t, 4H, CH_2-N), 2.10-0.90 (broad signal, 13H, $(CH_2)_4$, NH, NH_2); ir (NaCl): 3400 cm^{-1} (st, NH); ms: m/e (relative intensity): 222 (2) (M + 1), 221 (7), ($M^{+\cdot}$), 136 (25), 121 (61), 106 (100), 104 (33), 92 (50), 91 (70), 77 (64), 86, 72, 58, 44.

N-(*o*-Aminobenzyl)-*N'*-phthaloyl-1,6-hexanediamine (XI).

A mixture of X (6.17 g, 27.9 mmoles) and anhydrous phthalic anhydride (4.13 g, 27.8 mmoles) was heated at 145° for 30 minutes with mechanical stirring. The product was then dissolved in chloroform and 2 *N* hydrochloric acid was added. The aqueous layer was basified with 2 *N* sodium hydroxide and extracted with chloroform. The resulting organic layer was dried over anhydrous magnesium sulfate and evaporated to give XI (4.22 g, 43%); pmr: 7.79-7.31 (m, 4H, Ar-H), 7.10-6.39 (m, 4H, Ar-H), 5.20 (broad signal, 3H, NH), 3.67 (s, 2H, Ar-CH_2-N), 3.55 (broad signal, 2H, CH_2-N(CO)C_6H_4), 2.71-2.21 (t, 2H, CH_2-NH), 2.10-0.85 (broad signal, 8H $(CH_2)_4$); ir (chloroform): 3400 cm^{-1} (st, NH), 1789 and 1710 cm^{-1} (st, $N(CO)_2C_6H_4$).

N-(6-Aminohexyl)-1,2,3,4-tetrahydroquinazoline (II).

An aqueous solution of 40% formaldehyde (2.85 g, 32.9 mmoles) was added to a solution of XI (3.85 g, 10.9 mmoles) and potassium hydroxide (0.58 g, 10.5 mmoles) in methanol (30 ml). The mixture was stirred for 1 hour at reflux temperature. The solvent was removed under vacuum, the residue was dissolved in chloroform and washed several times with water. The organic layer was dried over anhydrous magnesium sulfate and evaporated to give XII as a yellow oil (3.78 g, 95%); pmr: 7.79-7.31 (m, 4H, Ar-H), 7.10-6.39 (m, 4H, Ar-H), 4.05 (s, 2H,N-CH_2-N), 3.85 (s, 2H, Ar-CH_2-N), 3.70-3.31 (m, 3H, CH_2-N(CO)$_2C_6H_4$), 2.45 (t, 2H, CH_2N), 1.18-1.10 (broad signal, 8H, $(CH_2)_4$, ir (chloroform): 3400 cm^{-1} (st, NH), 1780 and 1710 cm^{-1} (st, $N(CO)_2C_6H_4$).

This product was employed without purification in the next reaction. A solution of XII (2 g, 5.5 mmoles) and hydrazine monohydrate (0.82 g, 16.5 mmoles) in ethanol (100 ml) was refluxed and stirred for 3 hours. After this time, the solvent was removed and the residue treated with 2 *N*

sodium hydroxide and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and evaporated to give a mixture of XII and II which were separated by chromatography through a silica gel column. From 1.5 g of mixture, 0.64 g of XII on elution with benzene/chloroform 8:2, and 0.62 g of II (42%) on elution with chloroform/methanol 9:1, were obtained; pmr: 7.02-6.38 (m, 4H, Ar-H), 3.91 (s, 2H, NH-CH_2-N), 3.85 (s, 2H, Ar-CH_2-N), 3.60-3.23 (broad signal, 3H, NH, NH_2), 2.80-2.25 (m, 4H, CH_2-N), 1.71-1.08 (broad signal, 8H, $(CH_2)_4$); ir (chloroform): 3400 cm^{-1} (st, NH_2).

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