

Synthesis of 1,2-Disubstituted-1,4,5,6-tetrahydropyrimidines

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Cyclization of benzoyl derivatives of *N*-substituted trimethylenediamines with polyphosphoric acid or the corresponding ethyl ester, afforded 1,2-disubstituted-1,4,5,6-tetrahydropyrimidines. PPE was the more advantageous reagent. The excessive protonation of the starting material and the cleavage of the ether function produced by PPA explains the failure of this reagent to cause ring closure in some cases. Synthesis of the starting materials is described. Analytical and spectroscopic data of the new compounds are presented.

The principal methods used to prepare 2-substituted-1,4,5,6-tetrahydropyrimidines (1,2,3) are not satisfactory for the 1-aryl derivatives, because of the cumbersome synthesis and low yield of the necessary aryltrimethylenediamines. This may be the reason why no 1,2-diaryl derivatives have been reported so far in the literature.

Using an extension of a method used for imidazolines (4), we synthesized nine 1,2-diaryl-1,4,5,6-tetrahydropyrimidines with good results. The necessary *N*-aryl-*N'*-aroyltrimethylenediamines were obtained by two different ways (Scheme 1). Method A consisted in the reaction of *N*-(3-bromopropyl)benzamide with arylamines. Method B consisted of direct benzoylation of the corresponding

N-substituted 1,3-propanediamine. In method A arylamines functioned also as dehydrohalogenating agents. Yields were high (70-90%) for unsubstituted arylamines as well as for those containing electron donor substituents or weak electron acceptor groups. Yields were much lower for the *o*- and *p*-nitroanilines. In every case the corresponding *N,N*-bis(3-benzamidopropyl)arylamine (10-15%) was obtained as a secondary product. The latter alkylation of the *N*-aryl-*N'*-aroyltrimethylenediamines may account for the presence of the bis derivatives in the reaction. Yields for this derivative were lower when an excess of amine was used. Reaction products were separated according to their different solubilities in

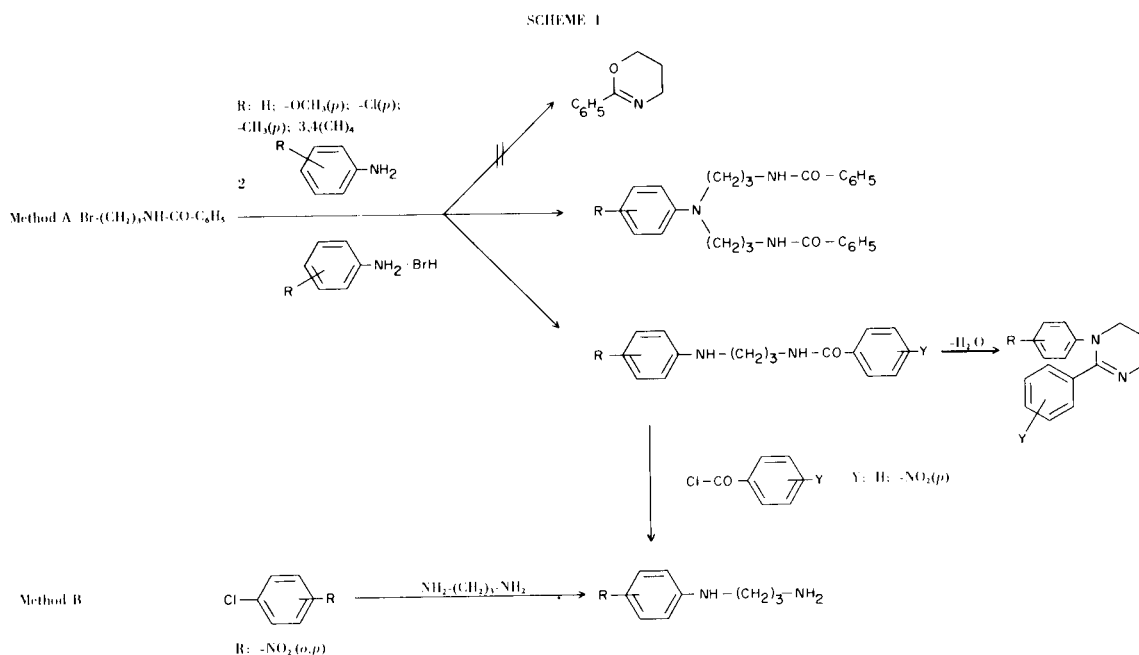





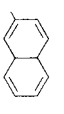





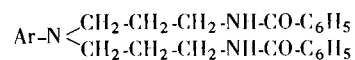






TABLE I
N-Substituted-*N'*-aroyltrimethylenediamines

Compound	R	Ar	Method	Yield %	M.p. °C	Recryst. Solvent	Formula	Anal.	C%	H%	N%	Mol. wt.
I	-C ₆ H ₅	-C ₆ H ₅	A	78	76	Cyclohexane	C ₁₆ H ₁₈ N ₂ O	Calcd.: Found:	75.6 75.5	7.09 6.89	11.02 11.27	254 247
II		-C ₆ H ₅	B	84	121	Methanol	C ₁₆ H ₁₇ N ₃ O ₃	Calcd.: Found:	64.2 64.3	5.68 5.85	14.05 14.18	299 308
III		-C ₆ H ₅	B	89	102	Ethanol	C ₁₆ H ₁₇ N ₃ O ₃	Calcd.: Found:	64.2 64.1	5.68 5.83	14.05 14.00	299 310
IV		-C ₆ H ₅	A	83	114	Methanol	C ₁₇ H ₂₀ N ₂ O ₂	Calcd.: Found:	71.8 71.6	7.04 7.18	9.86 9.83	284 272
V		-C ₆ H ₅	A	75	117	Methanol	C ₁₆ H ₁₇ ClN ₂ O (a)	Calcd.: Found:	66.5 66.5	5.89 5.74	9.70 9.68	288.5 301
VI		-C ₆ H ₅	A	90	123	Ethanol	C ₁₇ H ₂₀ N ₂ O	Calcd.: Found:	76.1 76.0	7.46 7.45	10.45 10.25	268 278
VII		-C ₆ H ₅	A	72	139	Methanol	C ₂₀ H ₂₀ N ₂ O	Calcd.: Found:	78.9 78.8	6.58 6.60	9.21 9.25	292 299
VIII			B	89	217	Dioxane	C ₁₆ H ₁₆ N ₄ O ₅	Calcd.: Found:	55.8 56.0	4.65 4.90	16.28 16.42	344 348
IX			B	91	160	Methanol	C ₁₆ H ₁₆ N ₄ O ₅	Calcd.: Found:	55.8 56.1	4.65 4.92	16.28 16.31	344 328
X		-C ₆ H ₅	A	42	52	(b)	C ₁₆ H ₂₄ N ₂ O	Calcd.: Found:	73.8 74.1	9.23 9.37	10.77 10.72	260 266

(a) Cl%, Calcd.: 12.31. Found: 12.50. (b) The oil obtained by distillation, solidified on standing.

TABLE II

N,N-Bis(3-benzamido)propylarylamines

Compound	Ar	M.p. °C	Recryst. Solvent	Formula	Anal.	C%	H%	N%	Mol. wt.
XI	-C ₆ H ₅	147	Ethyl acetate	C ₂₆ H ₂₉ N ₃ O ₂	Calcd.: Found:	75.2 75.2	6.99 7.09	10.12 10.13	415 420
XII		119	Benzene	C ₂₇ H ₃₁ N ₃ O ₃	Calcd.: Found:	72.8 72.6	6.97 6.74	9.44 9.62	445 460
XIII		151	Methanol	C ₂₆ H ₂₈ N ₃ O ₂ Cl (a)	Calcd.: Found:	69.4 69.3	6.23 6.42	9.34 9.55	449.5 440
XIV		146	Ethanol	C ₂₇ H ₃₁ N ₃ O ₂	Calcd.: Found:	75.5 75.7	7.22 7.05	9.79 9.95	429 414
XV		88	Benzene	C ₃₀ H ₃₁ N ₃ O ₂	Calcd.: Found:	77.4 77.3	6.67 6.84	9.03 9.13	465 476

(a) Cl%, Calcd.: 7.90. Found: 8.05.

TABLE III

Infrared Spectral Data of *N*-Substituted-*N'*-aroyltrimethylenediamines




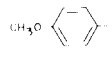



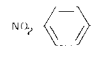
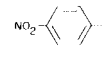

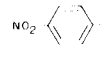

Compound	NH	Amide I	C=C	Amide II	C-N
I	3360(s)	1620(s)	1605(s) 1574(m)	1524(s)	1303(s)
II	3420(m) 3290(s)	1638(m)	1600(s) 1578(m)	1522(m)	1300(s)
III	3385(m) 3260(s)	1640(m)	1610(s) 1578(s)	1510(m)	1320(m)
IV	3424(s) 3350(s)	1660(s)	1610(m) 1590(m)	1525(m)	1305(m)
V	3438(s) 3330(s)	1660(s)	1610(s) 1590(m)	1520(s)	1295(m)
VI	3420(s) 3348(s)	1646(s)	1610(s) 1580(m)	1520(s)	1306(m)
VII	3450(s) 3378(s)	1650(s)	1600(m) 1570(s)	1510(m)	1315(m)
VIII	3410(s) 3325(s)	1640(s)	1600(s) 1580(m)	1518(s)	1318(s)
IX	3394(m) 3300(s)	1640(s)	1610(s) 1577(m)	1510(s)	1300(s)
X	3460(m) 3260(m)	1660(s)	1590(m)	1520(s)	1310(s)

TABLE IV

Infrared Spectral Data of *N,N*-Bis(3-benzamidopropyl)arylamines

Compound	NH	Amide I	C=C	Amide II	C-N
XI	3318(s)	1640(s)	1604(s) 1580(m)	1505(s)	1310(s)
XII	3330(s)	1636(s)	1600(m) 1579(m)	1515(m)	1308(m)
XIII	3319(s)	1642(s)	1603(m) 1588(m)	1510(s)	1316(m)
XIV	3300(s)	1630(s)	1600(m) 1579(m)	1518(s)	1307(s)
XV	3320(s)	1648(s)	1595(m)	1526(s)	1305(m)

TABLE V
Cyclization of *N*-Substituted-*N'*-aroyltrimethylenediamines

R-NH-(CH ₂) ₃ -NH-CO-Ar		$\xrightarrow{\text{H}_2\text{O}}$ 		
R	Ar	PPA 2 hours 150° Yield %	PPE 2 hours 62° Yield %	POCl ₃ 105° Yield %
-C ₆ H ₅	-C ₆ H ₅	79	95	
	-C ₆ H ₅	88	100	
	-C ₆ H ₅	85	100	
	-C ₆ H ₅	0 (a)	95	59 (b)
	-C ₆ H ₅	80	96	
	-C ₆ H ₅	50	89	
	-C ₆ H ₅	90	92	
		79	95	
		85	98	
	-C ₆ H ₅	0 (c)	75 (d)	68 (e)












(a) Starting material is not recovered. (b) Heating 2 hours. (c) Starting material is quantitatively recovered. (d) Heating 14 hours. (e) Heating 4 hours.

organic solvents or dilute acids. Intramolecular dehydrohalogenation of the *N*-(3-bromopropyl)benzamide was never observed. When a more basic amine such as cyclohexylamine was used, yields for the substitution product were notably lower (42% of *N*-cyclohexyl-*N'*-benzoyltrimethylenediamine) and a considerable amount of 2-phenyl-4,5-dihydro-6*H*-1,3-oxazine (38%) was obtained by intramolecular dehydrohalogenation. For the synthesis of the *o*- and *p*-nitrophenyl derivatives, direct benzoylation of the corresponding *N*-substituted-1,3-propanediamine was performed (Method B).

The *N*-substituted-*N'*-aroyltrimethylenediamines I to X (listed in Table I) and the *N,N*-bis(3-benzamidopropyl)-arylamines XI to XV (listed in Table II) were identified by elementary analysis, molecular weights and ir spectra (see Tables III and IV).

Cyclization was performed with polyphosphoric acid (PPA) at 150° or with the corresponding ethyl ester (PPE) in chloroform solution, in a 1 to 15 ratio by weight. The use of PPE was preferred because yields were better and conditions smoother than with PPA. This can be explained taking into account the mechanism generally accepted for

TABLE VI
1,2-Disubstituted-1,4,5,6-tetrahydropyrimidines

Compound	R	Ar	Bases M.p. °C	Recryst. Solvent	Salts M.p. °C	Formula Bases	Anal.	C%	H%	N%	Cl%
XVI	-C ₆ H ₅	-C ₆ H ₅	68	n-Hexane	Picrate 166	C ₁₆ H ₁₆ N ₂	Calcd.: Found:	81.4 81.2	6.78 6.58	11.86 11.99	
XVII		-C ₆ H ₅	129	Cyclohexane	Picrate 170	C ₁₆ H ₁₅ N ₃ O ₂	Calcd.: Found:	68.3 68.5	5.34 5.53	14.94 14.90	
XVIII		-C ₆ H ₅	102	Cyclohexane	Picrate 171	C ₁₆ H ₁₅ N ₃ O ₂	Calcd.: Found:	68.3 68.5	5.34 5.58	14.94 14.89	
XIX		-C ₆ H ₅	52	(a)	Chloroplatinate 205	C ₁₇ H ₁₈ N ₂ O	Calcd.: Found:	76.7 76.4	6.77 6.92	10.52 10.38	
XX		-C ₆ H ₅	105	Cyclohexane	Picrate 166	C ₁₆ H ₁₅ ClN ₂	Calcd.: Found:	71.0 71.0	5.54 5.48	10.35 10.40	13.12 13.00
XXI		-C ₆ H ₅	oil		Chloroplatinate 218	C ₃₄ H ₃₈ Cl ₆ N ₄ Pt (b)	Calcd.: Found:	44.8 44.7	4.17 3.90	6.15 6.30	23.41 23.60
XXII		-C ₆ H ₅	142	Cyclohexane	Picrate 168	C ₂₀ H ₁₈ N ₂	Calcd.: Found:	83.9 83.7	6.29 6.31	9.79 9.72	
XXIII			186	Methanol	Picrate 238	C ₁₆ H ₁₄ N ₄ O ₄	Calcd.: Found:	58.9 58.7	4.29 4.50	17.18 17.20	
XXIV			153	Methanol	Chloroplatinate 248	C ₁₆ H ₁₄ N ₄ O ₄	Calcd.: Found:	58.9 58.8	4.29 4.35	17.18 17.34	
XXV		-C ₆ H ₅	oil		Chloroplatinate 243	C ₃₂ H ₄₆ Cl ₆ N ₄ Pt	Calcd.: Found:	42.9 42.6	5.15 5.32	6.26 6.42	23.82 23.66

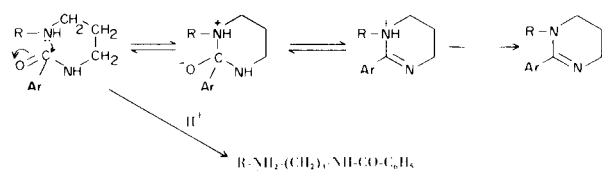
(a) The base recently purified is an oil that solidified on standing. (b) The base is an oil, analyzed as chloroplatinate.

TABLE VII
Infrared Spectral Data of 1,2-Disubstituted-1,4,5,6-tetrahydropyrimidines

Compound	XVI	1623(s)	1602(s)	1582(m)	1503(s)	1480(m)	1458(m)	1366(s)	1275(m)	1110(m)
Compound	XVII	1623(s)	1600(s)	1580(s)	1490(s)	1470(m)	1460(m)	1360(s)	1260(s)	1104(s)
Compound	XVIII	1625(s)	1605(s)	1580(m)	1510(m)	1488(m)	1450(m)	1360(s)	1275(m)	1110(m)
Compound	XIX	1620(s)	1605(s)	1580(s)	1510(s)	1500(m)	1450(m)	1365(s)	1260(s)	1118(m)
Compound	XX	1625(s)	1600(s)	1578(s)	1500(s)	1485(s)	1456(s)	1356(s)	1275(s)	1110(s)
Compound	XXI	1625(s)	1600(vs)	1580(s)	1510(m)	1480(w)	1453(m)	1368(s)	1270(m)	1110(w)
Compound	XXII	1625(s)	1600(s)	1585(s)	1505(m)	1480(m)	1460(m)	1360(s)	1280(s)	1115(m)
Compound	XXIII	1625(m)	1602(s)	1590(s)	1500(s)	1488(m)	1472(m)	1350(s)	1274(s)	1105(m)
Compound	XXIV	1630(s)	1603(vs)	1584(m)	1490(m)	1480(m)	1460(m)	1368(s)	1280(m)	1100(m)
Compound	XXV	1625(s)	1600(s)	1585(m)	1500(w)	1480(w)	1455(m)	1375(m)	1260(m)	1090(w)

Data in cm^{-1} : w = weak; m = medium; s = strong; vs = very strong.

this type of reactions which involve a nucleophilic attack by the aminic nitrogen on the carbonyl carbon (5).



Protonation of the amino group by PPA results in the requirement of stronger conditions to produce cyclization. Some reports have been made about the failure of PPA to cause ring-closure due to the excessive protonation produced by this reagent (6,7). The less acidic PPE does not present this problem that is greater when the basicity of the secondary amine increases (see Table V). With the *N*-tolyl-*N'*-benzoyltrimethylenediamine under the specified conditions only half was transformed. With the cyclohexyl derivative, using PPA at 150° , the starting material was completely recovered. With PPE in chloroform solution, 12-14 hours were required to complete the reaction. Complete failure was observed when PPA was used for the anisyl derivative. This occurs because in the experimental conditions needed for the cyclization (temperature higher than 120°) PPA produces the cleavage of the ether function and the phenolic hydroxyl group is transformed into phosphoric ester which is soluble in aqueous medium at any pH. At lower temperatures the starting material was recovered. The cleavage of the ether function with PPA had already been observed in the synthesis of 1-(*p*-alkoxyphenyl)-2-phenyl-2-imidazolines (8) and other cyclic molecules (9). With the less acidic reagent phosphorus oxychloride, good results were obtained for the synthesis in which PPA did not work.

The structure of tetrahydropyrimidines XVI to XXV

(listed in Table VI) was confirmed by elementary analysis of the bases as solids and their picrates or chloroplatinates, and by ir and nmr spectra of the bases (Tables VII and VIII).

EXPERIMENTAL

All melting points are uncorrected and were taken on a Buchi Capillary melting point apparatus. Molecular weights were determined by the micro-Rast method (*d*-camphor). Ir spectra were recorded with a Beckman 20A instrument using potassium bromide pellets of the compounds with the exception of compounds X, XIX, XXI and XXV that were determined in 3-5% chloroform solutions in 0.5 mm cells. Nmr spectra were measured in deuteriochloroform with a 60-Mc Perkin Elmer R 12 spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal TMS reference. The abbreviations: S for singlet; D for doublet; T for triplet; Q for quartet; q for quintuplet and M for multiplet are used.

N-(*p*-Nitrophenyl)trimethylenediamine.

A mixture of 15 g. (0.095 mole) of *p*-chloronitrobenzene and 74 g. (0.1 mole) of 1,3-diaminopropane was refluxed in an oil bath at $135-140^\circ$ for one hour. The excess of diamine was removed *in vacuo* and the residue was dissolved in boiling dilute hydrochloric acid. The solution was filtered to remove any insoluble material (bis derivative) and made alkaline with 30% sodium hydroxide. The precipitate was filtered, washed with water and crystallized from ethanol-water, m.p. 111° , yield, 84%.

Anal. Calcd. for $\text{C}_9\text{H}_{13}\text{N}_3\text{O}_2$: C, 55.4; H, 6.67; N, 21.54. Found: C, 55.2; H, 6.80; N, 21.39.

N-(*p*-Nitrophenyl)-*N'*-benzoyltrimethylenediamine (II) (Method B).

A solution of 1.95 g. (0.01 mole) of *N*-(*p*-nitrophenyl)trimethylenediamine in 50 ml. of chloroform was refluxed for two hours with 1.50 ml. (0.013 mole) of benzoyl chloride and 2.25 ml. (0.016 mole) of triethylamine. The solvent was removed *in vacuo* and the solid residue was washed with 10% sodium hydroxide, dilute hydrochloric acid and water and crystallized, yield, 87%.

N-(*o*-Nitrophenyl)trimethylenediamine Hydrochloride.

This compound was prepared by a procedure similar to that

TABLE VIII
Nuclear Magnetic Resonance

Compound	R	Ar	ppm	Multiplicity	Assignment
XVI	-C ₆ H ₅	-C ₆ H ₅	2.00	(q)	-CH ₂ - (a)
			3.51-3.92	(Q)	-CH ₂ - (b)
			6.75-7.55	(M)	aromatic H
XVII		-C ₆ H ₅	2.03	(q)	-CH ₂ - (a)
			3.57-3.98	(Q)	-CH ₂ - (b)
			6.81	(D)	2 x H ₁
			7.10-7.50	(M)	-C ₆ H ₅
			7.91	(D)	2 x H ₂
XVIII		-C ₆ H ₅	2.05	(q)	-CH ₂ - (a)
			3.60-3.90	(M)	-CH ₂ - (b)
			7.63-7.84	(Q)	H ₁
			6.92-7.54	(M)	the remaining H
XIX		-C ₆ H ₅	2.00	(q)	-CH ₂ - (a)
			3.50-3.83	(M)	-CH ₂ - (b)
			3.63	(S)*	-O-CH ₃
			6.45-6.90	(M)	-O-C ₆ H ₄ -
			6.95-7.45	(M)	-C ₆ H ₅
XX		-C ₆ H ₅	1.95	(q)	-CH ₂ - (a)
			3.40-3.90	(M)	-CH ₂ - (b)
			6.40-7.41	(M)	aromatic H
XXI		-C ₆ H ₅	1.85-2.19	**	-CH ₂ - (a)
			2.17	(S)	-CH ₃
			3.46-3.86	(M)	-CH ₂ - (b)
			6.60-6.90	(M)	-C ₆ H ₄ -
			6.95-7.50	(M)	-C ₆ H ₅
XXII		-C ₆ H ₅	2.00	(q)	-CH ₂ - (a)
			3.55-4.00	(Q)	-CH ₂ - (b)
			6.84-7.77	(M)	aromatic H
XXIII			2.08	(q)	-CH ₂ - (a)
			3.61-4.02	(Q)	-CH ₂ - (b)
			6.85	(D)	2 x H ₁
			7.20-8.15	(M)	the remaining aromatic H
XXIV			2.08	(q)	-CH ₂ - (a)
			3.39-3.91	(M)	-CH ₂ - (b)
			8.04	(D)	2 x H ₁
			6.97-7.80	(M)	the remaining aromatic H
XXV		-C ₆ H ₅	0.50-2.20	(M)	-CH ₂ - (a), C ₆ H ₁₁ -
			3.00-3.70	(M)	-CH ₂ - (b)
			7.20-7.65	(M)	-C ₆ H ₅

* Overlap with -CH₂- (b). ** Multiplicity is not clear by overlapping with -CH₃.

for the *p*-isomer but it was isolated as the hydrochloride. The oily base was extracted with chloroform. The chloroform solution was washed, dried with anhydrous sodium sulfate and treated with ethereal hydrogen chloride solution. The resulting solid was washed with ether and crystallized from absolute ethanol or 2-propanol affording hygroscopic orange needles, m.p. 174°, yield, 79%.

Anal. Calcd. for C₉H₁₄ClN₃O₂: C, 46.6; H, 6.05; N, 18.14; Cl, 15.33. Found: C, 46.5; H, 6.12; N, 17.99; Cl, 15.50.

N-(*o*-Nitrophenyl)-*N'*-benzyltrimethylenediamine (III) (Method B).

A solution of 1.62 ml. (0.014 mole) of benzoyl chloride in 30 ml. of anhydrous acetone was added dropwise during one hour to a stirred cooled suspension of 2.31 g. (0.01 mole) of *N*-(*o*-nitrophenyl)trimethylenediamine hydrochloride in 40 ml. of 5% sodium hydroxide and 15 ml. of acetone. Stirring was continued for two hours and the mixture was poured into water and filtered.

The resulting solid was washed with dilute hydrochloric acid and water and crystallized.

N-(*p*-Nitrophenyl)-*N'*-(*p*-nitrobenzoyl)trimethylenediamine (VIII) (Method B).

p-Nitrobenzoyl chloride 2.23 g. (0.012 mole) and 2.81 ml. (0.02 mole) of triethylamine were added to a boiling solution of 1.95 g. (0.01 mole) of *N*-(*p*-nitrophenyl)trimethylenediamine in 100 ml. of chloroform. The mixture was refluxed for two hours and cooled. The solid was filtered, washed with dilute hydrochloric acid and water and crystallized.

N-(*o*-Nitrophenyl)-*N'*-(*p*-nitrobenzoyl)trimethylenediamine (IX) (Method B).

N-(*o*-Nitrophenyl)trimethylenediamine hydrochloride (2.31 g., 0.01 mole) was stirred with 30 ml. of chloroform and 20 ml. of 5% sodium hydroxide. The aqueous phase was decanted and extracted twice with 10 ml. of chloroform. The organic layers were collected and dried with anhydrous sodium sulfate. The chloroform solution of the base was treated with 2.23 g. (0.012 mole) of *p*-nitrobenzoyl chloride and 2.81 ml. (0.02 mole) of triethylamine and refluxed for two hours. The solvent was removed *in vacuo* and the solid residue was washed with 10% sodium hydroxide, dilute hydrochloric acid and water and crystallized.

N-Phenyl-*N'*-benzoyltrimethylenediamine (I) (Method A).

A mixture of 2.42 g. (0.01 mole) of *N*-(3-bromopropyl)benzamide (10) and 1.82 ml. (0.02 mole) of aniline, was heated in a water bath at 100° for one hour. The crude product was washed three times with boiling water. The oil was cooled and the resulting solid was crystallized from ethyl acetate affording 12% of XI. The remaining solution was concentrated and the residue crystallized from cyclohexane yielding 78% of I.

Compounds IV, V, VI and VII were synthesized by method A in a manner similar to that for compound I, varying only in the separation of the reaction products which was done according to their different solubilities in warm dilute hydrochloric acid. (Bis derivatives are generally insoluble under these conditions). The products were crystallized from the proper solvents (see Tables I and II).

N-Cyclohexyl-*N'*-benzoyltrimethylenediamine (X) (Method A).

A mixture of 12.1 g. (0.05 mole) of *N*-(3-bromopropyl)benzamide and 12.1 ml. (0.1 mole) of cyclohexylamine, was heated in a water bath at 100° for one hour. The crude product was washed three times with boiling water and the oil dissolved in chloroform. The organic solution was washed with 5% sodium hydroxide and water and dried with anhydrous sodium sulfate. The solvent was removed and the residue distilled under reduced pressure in a Vigreux column, giving 36% of 2-phenyl-4,5-dihydro-6*H*-1,3-oxazine (XXVI), b.p. 125-130° (10 mm) and 42% of X, b.p. 242-246° (10 mm) that solidified on standing, m.p. 52°.

Compound XXVI was transformed to the picrate, m.p. 152° (ethanol); mixture melting point with an authentic sample (10), 152°.

1,2-Diaryl-1,4,5,6-tetrahydropyrimidines (XVI to XXIV).

(a) With Polyphosphoric Acid Ethyl Ester (PPE).

N-Aryl-*N'*-aroyltrimethylenediamine (1 g.) was refluxed for two hours with 20 ml. of chloroform solution of PPE (11). The organic layer was extracted four times with water. Acid solutions were collected, cooled and made alkaline with 20% sodium hydrox-

ide. If the tetrahydropyrimidine precipitated, it was collected; if not, the suspension was extracted three times with 30 ml. of methylene chloride. The organic solution, after washing with water, was dried and evaporated *in vacuo*. Compounds XVI, XVII, XVIII, XX, XXII, XXIII and XXIV were purified by repeated crystallization from the proper solvents (see Table VI). Compounds XIX and XXI were purified by dissolving the crude product in dilute hydrochloric acid. The acid solution was brought to neutral pH with solid sodium carbonate and extracted with chloroform to remove basic products. The resulting aqueous solution was made strongly alkaline with 20% sodium hydroxide and extracted with methylene chloride. The organic extracts were properly washed, dried and concentrated *in vacuo* affording the pure base. Purity was checked by tlc.

(b) With Polyphosphoric Acid (PPA).

An intimate mixture of 1 g. of *N*-aryl-*N'*-aroyltrimethylenediamine and 10 g. of PPA (83% of phosphorus pentoxide) was placed in a closed tube and heated in an oil bath at 150° for two hours. The mixture was cooled and dissolved in 100 ml. of ice water. This solution was neutralized with solid sodium carbonate and extracted with chloroform to remove unchanged starting material. The aqueous solution was made strongly alkaline and the base isolated as above.

(c) With Phosphorus Oxychloride.

N-Aryl-*N'*-aroyltrimethylenediamine (1 g.) was refluxed for two hours with 15 ml. of phosphorus oxychloride. The excess reagent was removed by distillation under reduced pressure keeping the reaction flask in a water bath at 100°. The residue was dissolved in 100 ml. of ice water and the resulting aqueous solution was treated as indicated above.

1-Cyclohexyl-2-phenyl-1,4,5,6-tetrahydropyrimidine (XXV).

This compound was synthesized by the general procedure using either PPE or phosphorus oxychloride; with these reagents 14 and 4 hours of reflux were required, respectively. The oily base was purified as compounds XIX and XXI and isolated as the chloroplatinate (see Table VI).

Picrates were obtained dissolving the bases in dilute hydrochloric acid and precipitating with aqueous solution of picric acid. The resulting solids were crystallized from ethanol (see Table VI).

Chloroplatinates were obtained by addition of 10% aqueous chloroplatinic acid to a boiling solution of the base in ethanol. After cooling, the precipitate was filtered and washed with warm ethanol (see Table VI).

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