1,2,4-Triazino[4,3-*c*]- and [2,3-*c*]quinazolines. II (1).

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This paper describes the results of allowing a variety of reagents, such as, aldehydes, ketones, carboxylic acids, acid chlorides, ortho esters, isocyanates, *S*-methylisothiourea, carbon disulfide, phosgene, nitrous acid, and cyanogen bromide to react with the multifunctional compound, 3-(*o*-aminophenyl)-1-methyl-1,4,5,6-tetrahydro-1,2,4-triazine.

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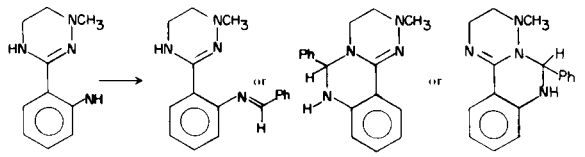


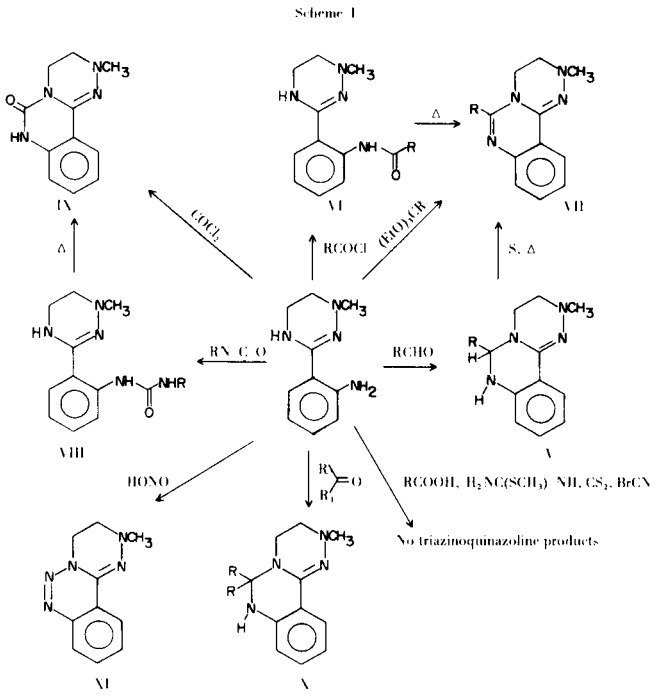
I II III IV

reaction of benzaldehyde with the primary amino group. Triazinoquinazolines III and IV are ring tautomers of the imine II. Ring tautomer III results from ring closure at N-4, the amine nitrogen of the 1,2,4-triazine ring, and ring tautomer IV results from ring closure at N-2, the hydrazine nitrogen of the 1,2,4-triazine ring. Since these condensations have not been reported and 1,2,4-triazino[4,3-*c*]- and [2,3-*c*]quinazolines are novel heterocyclic systems, it was of interest to determine the nature of the products from the various reactions, and furthermore, it was of interest to find out how to identify them; especially the two possible isomeric triazinoquinazolines.

It was found, as shown in Scheme I, that aldehydes reacted with I to give 6-substituted-3,4,6,7-tetrahydro-2-methyl-2*H*-1,2,4-triazino[4,3-*c*]quinazolines (V). Acid chlorides reacted with I to afford 3-(*o*-acylaminophenyl)-1,4,5,6-tetrahydro-1-methyl-1,2,4-triazines (VI), which could be thermally cyclodehydrated at 170-190° to yield 6-substituted-3,4-dihydro-2-methyl-2*H*-1,2,4-triazino[4,3-*c*]quinazolines (VII). This thermal cyclodehydration was retarded when there was an ortho substituent on the benzoylamino moiety of VI. For example, attempted thermal cyclodehydration of *o*-F, *o*-CH_3, and *o*-CH_3O substituted VI succeeded only in the case of *o*-F, and even with *o*-F rather poorly, as evidenced by only a 19% yield of triazino[4,3-*c*]quinazoline (VII). With *o*-CH_3 and *o*-CH_3O mostly unchanged starting material was recovered.

Isocyanates reacted with I to afford ureas (VIII) which were thermally cyclized to 2,3,4,7-tetrahydro-2-methyl-6*H*-1,2,4-triazino[4-3-*c*]quinazolin-6-one (IX) (1). This same triazinoquinazolinone was prepared from I and phosgene and I and ethyl chloroformate (1).

Scheme I



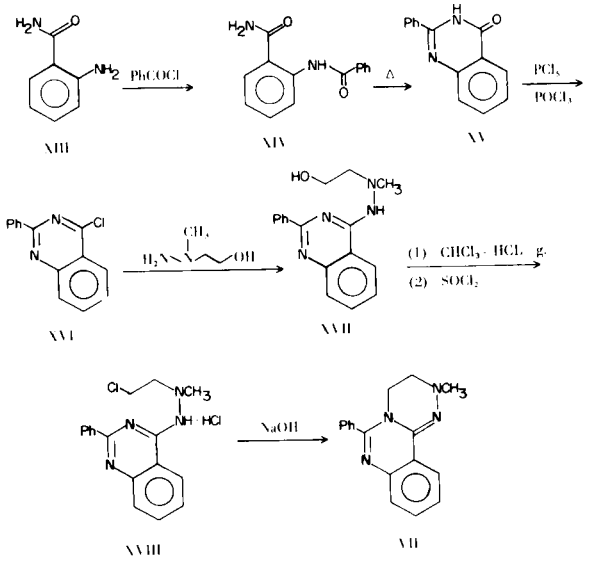
Ketones reacted with I to yield 6,6-disubstituted-3,4,6,7-tetrahydro-2-methyl-2*H*-1,2,4-triazino[4,3-*c*]quinazolines (X).

Nitrous acid reacted with I to give 3,4-dihydro-2-methyl-2*H*-benzo[*e*]-1,2,4-triazino[4,3-*c*]triazine (XI).

Benzoic acid, *S*-methylisothiourea, cyanogen bromide, and carbon disulfide were allowed to react with I and all failed to give a triazinoquinazoline product.

The structures assigned to the reaction products are based on the results of ir, uv, pmr, elemental analyses and unequivocal syntheses.

One of the key unequivocal syntheses was that for 3,4-dihydro-2-methyl-6-phenyl-2*H*-1,2,4-triazino[4,3-*c*]-quinazoline (VII, R = C_6H_5). Anthranilamide (XIII) was allowed to react with benzoyl chloride to give *N*-benzoylanthranilamide (XIV), which was thermally cyclized to 2-phenyl-4-quinazolinone (XV). Treatment of XV with phosphorus pentachloride-phosphorus oxytrichloride gave 4-chloro-2-phenylquinazoline (XVI). The 4-chloro-2-phenylquinazoline (XVI) was treated with *N*-β-hydroxyethyl-*N*-methylhydrazine to yield 4-(2-β-hydroxyethyl-2-methylhydrazino)-2-phenylquinazoline (XVII). Treatment of XVII with hydrogen chloride and then thionyl chloride converted it to 4-(2-β-chloroethyl-2-methylhydrazino)-2-phenylquinazoline hydrochloride (XVIII).



Sodium hydroxide cyclodehydrochlorination converted (XVIII) to authentic 3,4-dihydro-2-methyl-6-phenyl-2*H*-1,2,4-triazino[4,3-*c*]quinazoline (VII, R = C_6H_5).

This authentic VII, R = C_6H_5 served as a reference for assigning the structure of the aldehyde, ortho ester, and acid chloride condensation products. In the case of the reaction of I with aldehydes, the pmr spectra of the products contained a doublet around 5 ppm (J = 2.5 Hz) which collapsed to a sharp singlet upon deuterium oxide exchange indicating the product was either of the triazinoquinazolines III or IV and not imine II. Dehydrogenation of the condensation product of I and benzaldehyde (V, R-C_6H_5) by heating with elemental sulfur yielded 3,4-dihydro-2-methyl-6-phenyl-2*H*-1,2,4-triazino[4,3-*c*]quinazoline (VII, R = C_6H_5) indicating that, barring isomerization during the sulfur dehydrogenation, the aldehyde condensation products with I are triazino[4,3-*c*]quinazolines and not triazino[2,3-*c*]quinazolines.

Acid chlorides reacted with I to cause acylation of the primary aromatic amino group and yield 3-(acylamino)-1-methyl-1,4,5,6-tetrahydro-1,2,4-triazines (IV). That acylation had occurred at the primary aromatic amino group to yield IV and not the N-4 of the triazine ring is based on the fact that the pmr's of the products exhibited a rather sharp, definitive resonance peak around 6.7 ppm (in DMSO-d_6) indicative of an amide proton. If acylation had taken place on N-4 of the triazine ring, the products obtained would not have an amide proton. Heating the IV at 170-180° caused cyclodehydration to yield 3,4-dihydro-2-methyl-6-substituted-2*H*-1,2,4-triazino-[4,3-*c*]quinazolines (VII). That the pyrolysis products were VII was proven definitely only in the case where R = phenyl. It was assumed all others cyclodehydrated in an analogous manner to give triazino-[4,3-*c*]quinazolines (VII) and not the isomeric triazino[2,3-*c*]quinazolines.

Triethylorthobenzoate condensed with I to give triazino[4,3-*c*]quinazoline (VII) where R = phenyl. Triethyl orthoformate condensed with I to give a triazinoquinazoline. It was assumed that this too was the [4,3-*c*]-isomer.

Phenyl isocyanate and hydrocyanic acid were allowed to react with I to give ureas VIII, where R = phenyl and hydrogen. Heating these at 200° caused cyclization to 2,3,4,7-tetrahydro-2-methyl-6*H*-1,2,4-triazino[4,3-*c*]quinazolin-6-one (IX). The structure of IX was proved by an unequivocal synthesis (1). *o*-Aminothiobenzamide (XIX) was allowed to react with ethyl chloroformate in refluxing

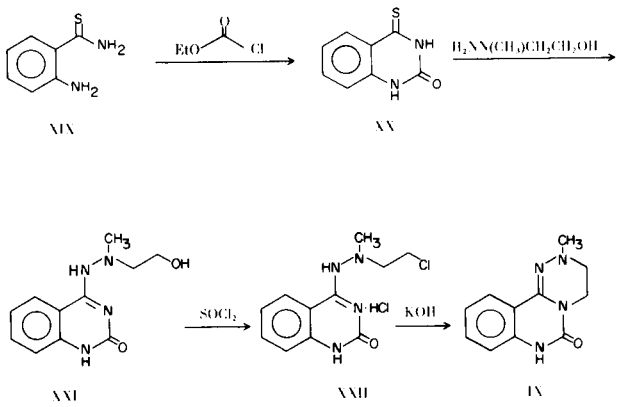
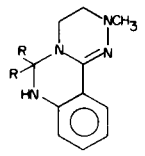


Table I

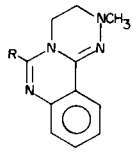
6-Substituted-2-methyl-3,4,6,7-tetrahydro-2*H*-1,2,4-triazino[4,3-c]quinazolines



No.	R	R_1	Method	Mp. °C	Recrystallization Solvent	% Yield	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	C_6H_5	H	A	204-205	i-PrOH	96	73.35	6.51	20.13	73.61	6.71	19.97
2	4-$(CH_3)_2NC_6H_4$	H	A	208-210	i-PrOH	78	70.99	7.21	21.79	70.20	7.52	21.32
3	3,4-$Cl_2C_6H_3$	H	A	189-190	EtOH	86	58.79	4.64	16.13	58.85	4.74	15.83
4	4-FC_6H_4	H	A	224-226	EtOH	92	68.89	5.78	18.90	69.01	6.00	18.61
5	3,4-$(CH_2O)_2C_6H_3$	H	A	172-178	EtOH	69	67.43	6.55	16.55	67.68	6.73	16.78
6	3,4-$(O_2N)_2C_6H_3$	H	A	213-124 dec.	EtOH	90	55.42	4.38	22.81	55.13	4.56	22.55
7	2-HOC_6H_4	H	A	156-158	EtOH	84	69.36	6.16	19.03	62.93	6.40	19.17
8	4-HOC_6H_4	H	A	223-224	EtOH	93	69.36	6.16	19.03	69.60	6.12	19.31
9	4-$CH_3CONHC_6H_4$	H	A	123-124.5	EtOH	89	68.03	6.31	20.80	67.32	6.69	20.33
10	$H_3C(CH_2)_4$	H	A	101-102	EtOH-Et_2O	56	70.55	8.88	20.57	70.79	8.88	20.39
11	$H_3C(CH_2)_5$	H	A	90-91	EtOH-Et_2O	51	71.28	9.15	19.56	71.00	9.15	19.47
12	4-$O_2NC_6H_4$	H	A	227-228	EtOH	83	63.14	5.30	21.66	63.58	5.30	21.84
13	3,4,5-$(CH_3O)_3C_6H_2$	H	A	189-191	EtOH	89	65.19	6.56	15.21	65.47	6.26	15.35
14	4-NC_5H_4	H	A	188.189.5	i-PrOH	80	68.79	6.13	25.07	68.49	6.23	24.80
15	2-NC_5H_4	H	A	143-145	i-PrOH	78	68.79	6.13	25.07	68.57	6.10	25.03
16	C_6H_5	CH_3	B	206-108	EtOH	71	73.94	6.89	19.16	73.72	6.85	19.14
17	4-HOC_6H_4	CH_3	B	238-140	EtOH	57	70.10	6.53	18.16	69.94	6.80	18.10
18	4-$(CH_3)_2CHC_6H_4$	H	A	190-191	i-PrOH	91	74.96	7.55	17.48	75.23	7.32	17.56
19	β-Naphthyl	CH_3	B	193-194	EtOH	56	77.16	6.47	16.36	77.24	6.63	16.47
20	$(CH_3)_2CH$	H	A	128-130	EtOH	73	68.81	8.25	22.93	68.52	8.03	22.66
21	3-NC_5H_4	H	A	155-156	EtOH	64	68.79	6.13	25.07	68.74	6.30	25.21
22	4-FC_6H_4	CH_3	B	198.5-200	EtOH	70	60.65	6.17	18.20	69.72	6.31	18.05
23	4-$Et_2N(CH_2)_2OC_6H_4$	H	A	151.5-153	i-PrOH	74	70.19	7.94	17.79	70.47	7.66	17.93

Table II

6-Substituted-3,4-dihydro-2-methyl-2*H*-1,2,4-triazino[4,3-c]quinazolines

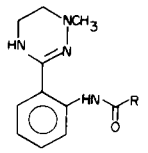


No.	R	M.p.,°C (a)	Yield, % (b)	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
24	2-FC_6H_4	132-133	19	69.37	5.13	19.03	69.60	5.11	19.10
25	4-FC_6H_4	157-158	74	69.37	5.13	19.03	69.65	5.03	18.97
26	4-$CH_3C_6H_4$	134-135	64	74.45	6.24	19.29	74.55	6.38	19.42
27	4-NCC_6H_4	189-190	90	71.73	5.01	23.24	71.46	4.99	22.98
28	3-BrC_6H_4	186-187	79	57.47	4.25	15.77	57.23	4.49	15.62
29	4-BrC_6H_4	183-184	69	57.47	4.25	15.77	57.41	4.51	15.81
30	3,4,5-$(CH_3O)_3C_6H_2$	186-187	80	65.55	6.05	15.29	65.59	6.19	15.01
31	3,4-$Cl_2C_6H_3$	184-185	72	59.14	4.08	16.23	59.19	4.21	16.08
32	C_6H_5	142-143	74	73.88	5.83	20.27	73.62	5.73	19.99
33	H	55-56	71	65.97	6.04	27.98	66.16	6.19	28.18

(a) Compounds **25**, **27**, **28**, **29**, **30**, and **31** were recrystallized from ethanol, compounds **24**, **26**, and **32** from 2-propanol, and compound **33** from ethyl ether. (b) Compounds **24-31** were prepared using Method A. Compound **32** was prepared by Methods A and B. Compound **33** was prepared using Method B.

Table III

3-(*o*-Acylaminophenyl)-1-methyl-1,4,5,6-tetrahydro-1,2,4-triazines



No.	R	M.p. °C (a)	Yield, %	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
34	C_6H_5	125-126	72	69.36	6.16	19.03	69.31	6.38	18.73
35	$3,4\text{-}Cl_2C_6H_3$	162-163	73	56.20	4.44	15.42	56.04	4.63	15.21
36	$3\text{-}BrC_6H_4$	167-168	85	54.69	4.59	15.01	54.57	4.71	15.00
37	$4\text{-}BrC_6H_4$	166-167	91	54.69	4.59	15.01	54.50	4.62	14.91
38	$4\text{-}O_2NC_6H_4$	219-221	76	60.16	5.05	20.63	60.01	5.07	20.35
39	$4\text{-}NCC_6H_4$	206-208	72	67.69	5.36	21.93	67.71	5.25	21.68
40	$2\text{-}CH_3C_6H_4$	118-119	67	70.10	6.53	18.16	70.35	6.51	18.41
41	$2\text{-}CH_3OC_6H_4$	150-152	73	66.64	6.21	17.27	66.91	6.22	16.96
42	$3,4,5\text{-}(CH_3O)C_6H_2$	111-113	67	62.48	6.29	14.57	62.25	6.58	14.45
43	$4\text{-}FC_6H_4$	142-144	73	65.36	5.48	17.93	65.60	5.67	17.99

(a) Compound **43** was recrystallized from 2-propanol and all others from ethanol.

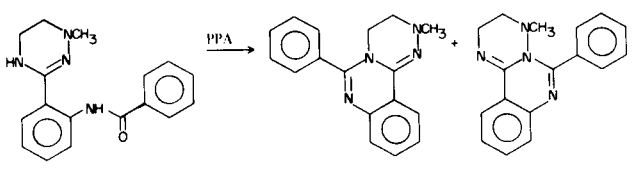
pyridine to afford 1,2,3,4-tetrahydroquinazolin-2-one-4-thione (XX), which on treatment with 1-methyl-1-(β-hydroxyethyl)hydrazine gave 1,2-dihydro-4-(2-β-hydroxyethyl-2-methylhydrazino)quinazolin-2-one (XXI). Treatment of XXI with thionyl chloride afforded 1,2-dihydro-4-(2-β-chloroethyl-2-methyl-hydrazino)quinazolin-2-one hydrochloride (XXII). Base catalyzed cyclodehydrochlorination of XV gave triazinoquinazolinone (IX).

Condensation of ketones with I afforded 2-methyl-3,4,6,7-tetrahydro-6,6-disubstituted-2*H*-1,2,4-triazino-[4,3-*c*]quinazolines (X). However, this condensation requires more forcing conditions (*p*-TsOH, azeotropic removal of water) than does the analogous condensation of I with aldehydes, which proceeds readily upon heating for a short time in ethanol. The structure of the ketone condensation products was assigned based on a comparison of the ultraviolet spectra of the ketone condensation products (X) with the corresponding aldehyde condensation products (V). They are paractically identical. For example, 2-methyl-3,4,6,7-tetrahydro-6-phenyl-2*H*-1,2,4-triazino[4,3-*c*]quinazoline (V, R = C_6H_5) exhibited λ max (methanol) at 220 and 335 nm with absorptivities of 11.15 and 2.27, and 2-methyl-3,4,6,7-tetrahydro-6-methyl-6-phenyl-2*H*-1,2,4-triazino[4,3-*c*]quinazoline (X, R = C_6H_5, R_1 = CH_3) exhibited λ max (methanol) at 220 and 335 nm with absorptivities of 10.95 and 2.15. This would not be the case if the ketone condensation products were the isomeric triazino[2,3-*c*]quinazolines, since then the double bond in conjugation with the phenyl ring would be an imine double bond instead of a hydrazone double bond and the chromophore would be markedly different resulting in different ultraviolet absorption.

Nitrosation of I with nitrous acid at 0-5° resulted in the formation of 3,4-dihydro-2-methyl-2*H*-1,2,4-triazino-[4,3-*c*]benzo-1,2,3-triazine (XI). An unequivocal synthesis of XI has not been accomplished. Therefore, the assignment of XI as the [4,3-*c*] isomer and not the [2,3-*c*] isomer is based entirely on the fact that all the afore mentioned condensations afforded the [4,3-*c*] isomer.

Attempted formation of triazinoquinazolines by allowing I to react with either benzoic acid, S-methylisothiourea, carbon disulfide, or cyanogen bromide all failed.

An investigation of the polyphosphoric acid catalyzed cyclodehydration of 3-(*o*-benzoylaminophenyl)-1-methyl-1,4,5,6-tetrahydro-1,2,4-triazine (VI, R = C_6H_5) showed that a mixture of 3,4-dihydro-2-methyl-6-phenyl-2*H*-1,2,4-triazino[4,3-*c*]quinazoline (VII, R = C_6H_5) and 3,4-



VI VII, yellow crystals m.p. 142-144° XXIII, white crystals m.p. 206-207°

dihydro-4-methyl-6-phenyl-2*H*-1,2,4-triazino[2,3-*c*]quinazoline (XXIII) was formed. The composition of the mixture changed with a change in the reaction temper-

ature. At 25° the product composition was 40% VII and 60% XXIII, and at a reaction temperature of 100° the product composition was 60% VII and 40% XXIII. The product mixtures were analyzed by glc, and isomers VII and XXIII were separated by column chromatography on silica gel 60-200 M using ethyl acetate as an eluant. Compound VII is yellow colored and compound XXIII is white. Compound XXIII may be devoid of color due to nonbonded interactions between the methyl group at position four and the phenyl moiety at position six preventing the phenyl from attaining coplanarity with the rest of the conjugated unsaturated system. This nonbonded interaction can also be see by comparing the nmr's of VII and XXIII. The five protons of the phenyl group in VII appear as a singlet indicating free rotation of the phenyl, whereas, the five protons of the phenyl group in XXIII appear as a multiplut indicating hindered rotation.

Biological Activity.

The triazinoquinazolines listed in Tables I and II were all tested for central nervous system activity in the mouse using the hydrochloric acid writhing, hexobarbital sleep time, and reserpine ptosis tests. These test methods have been described (2). Compounds **1**, **26**, and **33** were active in the hydrochloric acid writhing test indicating potential analgetic - antiinflammatory activity. Compounds **4**, **7**, **11**, **14**, **15**, **24**, **27**, **29**, **32**, and **33** were active in prolonging hexobarbital sleep time in mice. This is an indication of central nervous system depressant activity. Compounds **2**, **3**, **4**, **9**, **10**, **12**, **15**, **28**, and **33** were active in the reserpine ptosis test. Antagonism of reserpine induced ptosis in mice is a widely used test for detection of compounds possessing antidepressant activity. In summary, this series of dihydro- and tetrahydro-1,2,4-triazino[4,3-c]quinazolines exhibits central nervous system activity which is manifested in potentiating the effect of hexobarbital in mice and antagonizing the effect of reserpine and hydrochloric acid. In these three tests compound **33** showed the best activity profile.

EXPERIMENTAL

The melting points were obtained in a capillary tube with the Thomas-Hoover Uni-Melt and are uncorrected. The elemental analyses were done by Midwest Microlabs, Inc., Indianapolis, Indiana. The pmr spectra were obtained with a Varian A-60 using TMS as an internal standard. Infrared spectra were obtained with a Perkin-Elmer 337 grating spectrophotometer. Ultraviolet spectra were obtained on a Carey recording spectrophotometer.

General Methods for the Preparation of Tetrahydro-1,2,4-triazino-[4,3-c]quinazolines Listed in Table I.

Method A.

An ethanolic solution of equimolar quantities of 3-(*o*-aminophenyl)-2-methyl-1,4,5,6-tetrahydro-1,2,4-triazine (I) and an aldehyde was heated under reflux for 6 hours, cooled, the solid filtered and recrystallized from an appropriate solvent.

Method B.

A mixture of equimolar amounts of I and a ketone, 1.0 g. of *p*-toluenesulfonic acid, and 250 ml. of benzene was heated under reflux for 18 hours, and the azeotroped water separated with a Dean-Stark trap. The cooled mixture was washed with dilute sodium carbonate solution, water, dried over magnesium sulfate, and evaporated *in vacuo*. The residual solid was recrystallized from an appropriate solvent.

General Method for the Preparation of the Dihydro-1,2,4-triazino-[4,3-c]quinazolines Listed in Table II.

Method A.

A 10 g. portion of the 3-(*o*-acylaminophenyl)-1-methyl-1,4,5,6-tetrahydro-1,2,4-triazine (VI) was heated in an oil bath at 180-200° for 1 hour. After cooling the residue was recrystallized from an appropriate solvent.

Method B.

A mixture of equimolar amounts of I and an orthoester was heated under reflux for 18 hours. After cooling the residue was recrystallized from an appropriate solvent.

General Method of Preparation of the 3-(*o*-Acylaminophenyl)-1,4,5,6-tetrahydro-1,2,4-triazines (VI) Listed in Table III.

To a stirred mixture of 0.1 mole of I, 15 ml. of triethylamine, and 300 ml. of methylene chloride was added, dropwise, a solution of 0.1 mole of carboxylic acid chloride in methylene chloride. The mixture was stirred and heated at reflux temperature for 6 hours, cooled, washed with water, dried over magnesium sulfate, and evaporated *in vacuo*. The residual solid was recrystallized from an appropriate solvent.

Sulfur Catalyzed Dehydrogenation of 2-Methyl-6-phenyl-3,4,6,7-tetrahydro-2*H*-1,2,4-triazino[4,3-c]quinazoline (V) to give 3,4-Dihydro-2-methyl-6-phenyl-2*H*-1,2,4-triazino[4,3-c]quinazoline (VII, R = C_6H_5).

A mixture of 5.7 g. of 2-methyl-6-phenyl-3,4,6,7-tetrahydro-2*H*-1,2,4-triazino[4,3-c]quinazoline (V, R = C_6H_5), 1.2 g. of sulfur, 50 ml. of *o*-dichlorobenzene, and 25 ml. of benzene was heated in an oil bath at 180° for 1 hour. The cooled, red colored mixture was extracted with diluted hydrochloric acid. The cooled acid extract was basified with cold sodium hydroxide solution and extracted with methylene chloride. The methylene chloride extract was washed with water, dried over magnesium sulfate, and evaporated *in vacuo*. The residual yellow solid was recrystallized twice from isopropyl alcohol to afford 3.7 g. (65%) 3,4-dihydro-2-methyl-6-phenyl-2*H*-1,2,4-triazino[4,3-c]quinazoline (VII, R = C_6H_5), m.p. 143-144°.

Nitrosation of I to give 3,4-Dihydro-2-methyl-2*H*-1,2,4-triazino-[4,3-c]benzo-1,2,3-triazine (XI).

To a stirred, cooled (~ 5°) solution of 3.8 g. (0.02 mole) of 3-(*o*-aminophenyl)-1-methyl-1,4,5,6-tetrahydro-1,2,4-triazine (I) in 75 ml. of 20% sulfuric acid was added, dropwise, a solution of 1.4 g. (0.02 mole) sodium nitrite in 25 ml. water. After addition complete, stirred at ~ 5° for 2 hours, then stirred at ambient temperature for 2 hours, and solid removed by suction filteration. Solid dissolved in methanol, basified with methanolic potassium hydroxide, diluted with water, and extracted with methylene chloride. The methylene chloride solution was washed with water, dried over magnesium sulfate, and evaporated *in vacuo*.

The orange colored solid was recrystallized twice from ethanol to give 2.4 g. (60%) of XI, m.p. 193-194° dec.; λ max (methanol): 213, 286, and 340 nm with absorptivities 12.3, 6.62, and 5.84, respectively.

Anal. Calcd. for $C_{10}H_{11}N_5$: C, 59.68; H, 5.51; N, 34.81. Found: C, 59.82; H, 5.73; N, 34.58.

Polyphosphoric Acid Catalyzed Cyclodehydration of 3-(*o*-Benzoylaminophenyl)-1-methyl-1,4,5,6-tetrahydro-1,2,4-triazine (VI, R = C_6H_5) to give a Mixture of 3,4-Dihydro-2-methyl-6-phenyl-2*H*-1,2,4-treazino[4,3-*c*]quinazoline (VII, R = C_6H_5) and 3,4-Dihydro-4-methyl-6-phenyl-2*H*-1,2,4-triazino[2,3-*c*]quinazoline (XXIII).

A mixture of 5.0 g. of VI (R = C_6H_5) and 65 g. of polyphosphoric acid was stirred and heated on a steam bath for 1 hour. The cooled mixture was mixed with ice water, basified with sodium carbonate, and extracted with chloroform. The chloroform extract was washed with water, dried over magnesium sulfate, and evaporated *in vacuo* to afford 4.3 g. of a 40:60 mixture of VII (R = C_6H_5) and XXIII (glc 260°, 5 ft SE30/-chromsorb W/AW). The mixture was separated on a 500 g. silica gel 60-200 M column using ethyl acetate as the eluant. First to be eluted was yellow crystalline VII (R = C_6H_5), m.p. 142-144°; pmr ($CDCl_3$) δ 2.78 (s, 3H, NCH_3), 2.78 (t, 2H, J = 5 Hz) 3.64 (t, 2H, J = 5 Hz) 7.3 (s, 5H, Ph), 7-8 ppm (m, 4H, Ph). This was followed by white crystalline XXIII, m.p. 206-207°; pmr (deuteriochloroform): δ 2.37 (s, 3H, NCH_3), 3.13 (m, 2H, CH_2), 3.65 (m, 2H, CH_2), 7.0-8.1 ppm (m, 9 aromatic H's).

Anal. Calcd. for $C_{17}H_{16}N_4$: C, 73.88; H, 5.83; N, 20.27. Found: C, 73.55; H, 5.73; N, 19.92.

N-Benzoyl Anthranilamide (XIV).

To a stirred mixture of 68 g. (0.5 mole) of anthranilamide, 60 ml. of triethylamine, and 1200 ml. of chloroform was added, dropwise, 70 g. (0.5 mole) of benzoyl chloride in 300 ml. of chloroform. The mixture was stirred and heated under reflux for 18 hours, cooled, treated with 1000 ml. of water, and the solid XIV removed by suction filtration to give 100 g. (83%), m.p. 211-213°.

2-Phenylquinazolin-4-one (XV).

A 48 g. (0.2 mole) portion of *N*-benzoylanthranilamide (XIV) in a flask under nitrogen was heated at 250° for 1 hour. The cooled residue crystallized when scratched in acetone to afford 39 g. (81%) of solid XV, m.p. 237-239°; lit. m.p. 232-235° (3).

4-Chloro-2-phenylquinazoline (XVI).

A mixture of 22 g. (0.1 mole) of 2-phenylquinazolin-3*H*-4-one (XV), 30 g. of phosphorus pentachloride, and 120 ml. of phosphorus oxychloride was heated under reflux for 2 hours, cooled, evaporated *in vacuo*, treated with ice water, basified with sodium carbonate solution, and extracted with methylene chloride. The methylene chloride solution was dried over magnesium sulfate and evaporated *in vacuo* to afford 17 g. (70%) of XVI, m.p. 124-126°; lit. 126-127° (4).

4-(2-β-Hydroxyethyl-2-methylhydrazino)-2-phenylquinazoline (XVII).

A mixture of 15 g. (0.06 mole) of XVI, 7 g. (0.008 mole) of *N*-β-hydroxyethyl-*N*-methylhydrazine, and 100 ml. of ethanol was heated under reflux for 4 hours, concentrated *in vacuo*, diluted with water, treated with sodium carbonate solution, and extracted chloroform. The chloroform solution was dried over magnesium sulfate and evaporated *in vacuo* to give 6.3 g. (36%) of XVII, m.p. 159-161°. The analytical sample from 2-propanol had m.p. 161.5-162.5°.

Anal. Calcd. for $C_{17}H_{18}N_4O$: C, 69.36; H, 6.16; N, 19.03. Found: C, 69.48; H, 6.18; N, 19.11.

Conversion of 4-(2-β-Hydroxyethyl-2-methylhydrazino)-2-phenylquinazoline (XVII) into 3,4-Dihydro-2-methyl-6-phenyl-2*H*-1,2,4-triazino[4,3-*c*]quinazoline (VII, R = C_6H_5).

A solution of 4 g. (0.14 mole) of XVII in 150 ml. of dry chloroform was treated with gaseous hydrogen chloride. The chloroform was evaporated *in vacuo*. The residual solid was treated with 100 ml. of thionyl chloride, and the mixture was heated under reflux for 2 hours. The thionyl chloride was evaporated *in vacuo*, benzene was added and the evaporation repeated. The residue was dissolved in ethanol, a solution of 3 g. of sodium hydroxide in 20 ml. of water was added, and the mixture was heated on a steam bath for 5 minutes. The cooled solution was diluted with brine and extracted with chloroform. The chloroform solution was evaporated *in vacuo* and the residue recrystallized twice from isopropyl alcohol to afford 2.1 g. (50%) of 3,4-dihydro-2-methyl-6-phenyl-2*H*-1,2,4-triazino[4,3-*c*]quinazoline, m.p. 142-143°.

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