

Quinazolo[3,4-c]-1,2,4-triazoles

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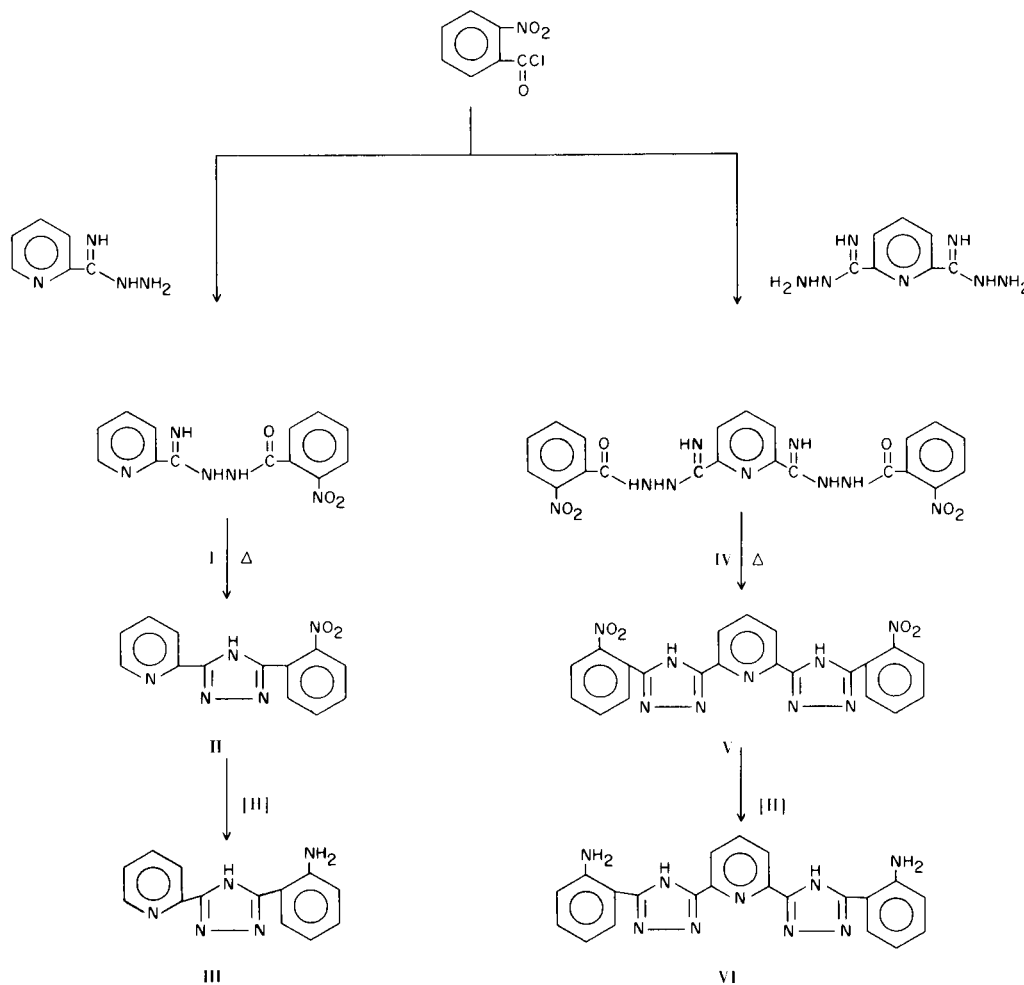
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As part of a program directed toward the preparation of heterocyclic polymers (1-5), it was of interest to synthesize a series of model compounds containing a novel heterocyclic fused ring system, quinazolo[3,4-c]-1,2,4-triazole. This work was performed to obtain information regarding reaction conditions necessary for the formation of polyquinazolotriazoles (5) and to obtain model compounds to aid in polymer identification.

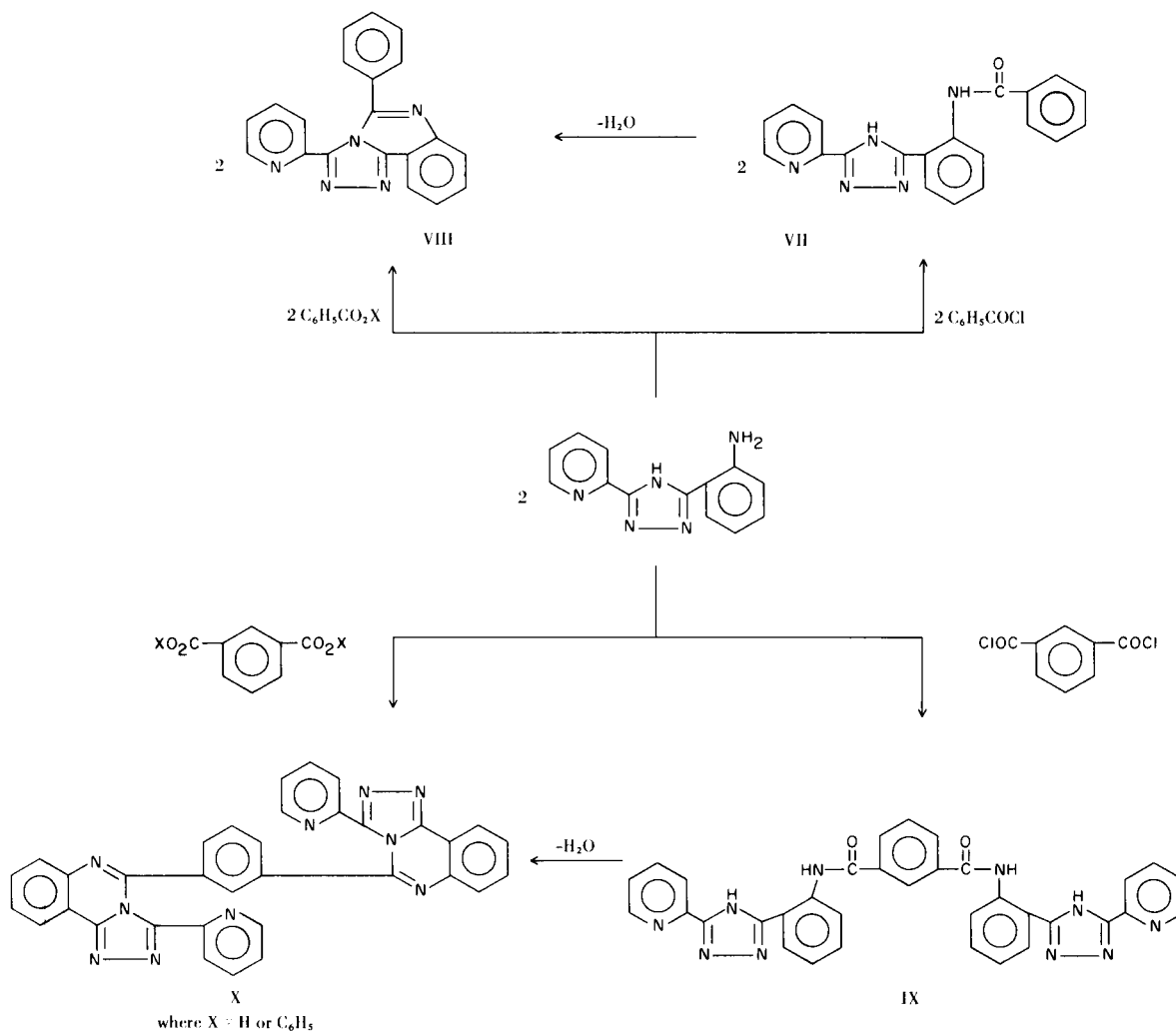
The 5-(*o*-aminophenyl)-1,2,4-triazole reactants for quin-

azolo[3,4-c]-1,2,4-triazole formation were prepared as shown in reaction scheme I. Reaction of the amidrazone (hydrazidine) in cold *N,N*-dimethylacetamide with *o*-nitrobenzoyl chloride provided the *N*-acylamidrazone in high yield (> 80%). The *N*-acylamidrazone can undergo cyclocondensation with the elimination of water and/or ammonia to form a 1,2,4-triazole and/or 1,3,4-oxadiazole respectively. As previously indicated (2,6), preferential formation of 1,3,4-oxadiazole can be accomplished by

REACTION SCHEME I



REACTION SCHEME II



REACTION SCHEME III

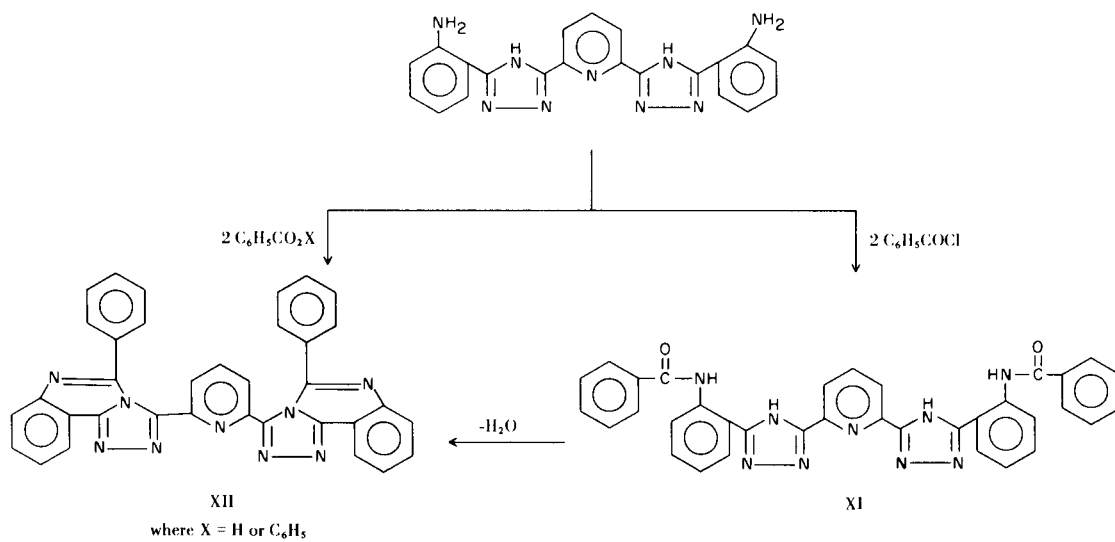


TABLE I
Characterization of Intermediates and Model Compounds

Compound Number	Compound	M.p., °C	Color	Formula	Elemental Analysis (a)	UV Spectrum (b)
					% C % H % N	λ max, $m\mu$ $\epsilon \times 10^{-3}$
I	<i>N</i> (<i>o</i> -nitrobenzoyl)(2-pyridyl)amidrazone	215-217 dec.	yellow solid	C ₁₃ H ₁₁ N ₅ O ₃	54.69 (54.73) 3.91 (3.89) 24.38 (24.55)	---
II	3-(2'-pyridyl)-5-(<i>o</i> -nitrophenyl)-1,2,4-triazole	191-192	tan cryst.	C ₁₃ H ₉ N ₅ O ₂	58.61 (58.42) 3.33 (3.39) 26.29 (26.21)	---
III	3-(2'-pyridyl)-5-(<i>o</i> -aminophenyl)-1,2,4-triazole	184-185.5	lt. tan cryst.	C ₁₃ H ₁₁ N ₅	66.06 (65.81) 4.59 (4.67) 29.45 (29.52)	---
IV	<i>N,N'</i> -di(<i>o</i> -nitrobenzoyl)(2,6-pyridinediyl) diamidrazone	160-162 dec.	yellow solid	C ₂₁ H ₁₇ N ₉ O ₆	50.68 (51.32) 4.41 (3.49) 24.33 (25.66)	---
V	3,3'-(2'',6''-pyridinediyl)bis[5-(<i>o</i> -nitrophenyl)-1,2,4-triazole]	311-312.5	tan cryst.	C ₂₁ H ₁₃ N ₉ O ₄	55.32 (55.38) 2.98 (2.88) 27.43 (27.69)	---
VI	3,3'-(2'',6''-pyridinediyl)bis[5-(<i>o</i> -aminophenyl)-1,2,4-triazole]	346-348	lt. tan to yel. cryst.	C ₂₁ H ₁₇ N ₉	63.73 (63.79) 4.45 (4.33) 31.95 (31.88)	---
VII	3-(2'-pyridyl)-5-(<i>o</i> -benzamidophenyl)-1,2,4-triazole	235-237 dec.	white solid	C ₂₀ H ₁₅ N ₅ O	69.89 (70.37) 4.55 (4.43) 20.84 (20.52)	250 286
VIII	2-phenylquinazol[3,4- <i>c</i>]-3-(2'-pyridyl)-1,2,4-triazole	186.5-187	white needles	C ₂₀ H ₁₃ N ₅	74.03 (74.29) 3.95 (4.05) 21.49 (21.66)	253 282 291 356
IX	isophthalamidobis[3-(2'-pyridyl)-5-(<i>o</i> -phenyl)-1,2,4-triazole]	289-291 dec.	yellow solid	C ₃₄ H ₂₄ N ₁₀ O ₂	67.33 (67.54) 4.18 (4.00) 23.07 (23.17)	240 286
X	5,5'-(<i>m</i> -phenylene)bis[quinazol[3,4- <i>c</i>]-3-(2'',6''-pyridyl)-1,2,4-triazole]	319-321	yellow needles	C ₃₄ H ₂₀ N ₁₀	71.68 (71.82) 3.47 (3.55) 24.56 (24.63)	253 284 291 346
XI	3,3'-(2'',6''-pyridinediyl)bis[5-(<i>o</i> -benzamidophenyl)-1,2,4-triazole]hydrate	202-205 dec.	yellow solid	C ₃₅ H ₂₇ N ₉ O ₃	67.31 (67.62) 4.30 (4.38) 20.17 (20.28)	258 300
XII	3,3'-(2'',6''-pyridinediyl)bis[5-phenylquinazol[3,4- <i>c</i>]-1,2,4-triazole]	264-264.5	white needles	C ₃₅ H ₂₂ N ₉	73.89 (73.92) 3.80 (3.90) 22.32 (22.17)	260 305 354

(a) Theoretical values in parenthesis. (b) Determined in sulfuric acid.

heating in strong acids such as trifluoroacetic acid. Whereas, conversion to the 1,2,4-triazole by refluxing in *m*-cresol is accompanied by the presence of a small amount (< 5%) of 1,3,4-oxadiazole. In this study, the 1,3,4-oxadiazole was removed by recrystallization and therefore

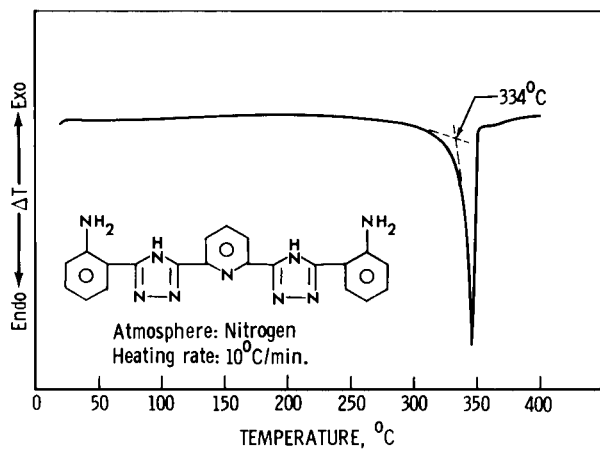


Figure 1. Differential Scanning Calorimetry of 3,3'-(2'',6''-pyridinediyl)bis[5-(*o*-aminophenyl)-1,2,4-triazole] (VI).

no serious problems were encountered in the purification of the nitro compounds (II and V). The reduction was accomplished in essentially quantitative crude yield using sodium sulfide nonahydrate in ethylene glycol at 115° or by hydrogenation at ambient temperature in methanol and/or pyridine under ~ 50 psi using Adams' catalyst. Compound VI exhibited a tenacious affinity for water and required drying for several hours at high temperature (200°) over phosphorus pentoxide *in vacuo* for removal. The melting point of compound VI as determined by differential scanning calorimetry (Figure 1) was 334° while the visual uncorrected melting point as determined on a Mel-Temp melting point apparatus was 346-348°.

Quinazolo[3,4-*c*]-1,2,4-triazoles were prepared as shown in reaction schemes II and III in essentially quantitative yields by the following three methods. The *o*-aminophenyl-1,2,4-triazole compounds (III and VI) were reacted with aromatic carboxylic acids by solution cyclodehydration in polyphosphoric acid at 250°, with phenyl esters of aromatic carboxylic acid by melt condensation to 340°, and with aromatic carboxylic acid chlorides to form precursor amides which were thermally cyclodehydrated at 300°. No chemical cyclodehydrating agents were employed in this study. The thermal cyclodehydration of 3-(2'-pyridyl)-5-(*o*-benzamidophenyl)-1,2,4-triazole (VII) was briefly studied by following the ring closure through infrared spectroscopy and melting point. At 250°, complete ring closure was not attained after 24 hours whereas at 300°, essentially complete ring closure

was observed after 1 hour. At 350°, complete ring closure occurred after 0.5 hour. Characterization of the quinazolo-triazole model compounds (VIII, X, and XII) is given in Table I while the ultraviolet spectra are shown in Figure 2.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. The ultraviolet spectra (in sulfuric acid) were obtained on a Cary 14 recording spectrophotometer while the differential scanning calorimetry curve was obtained on a Du Pont 900 thermal analyzer. Elemental analyses were determined by Galbraith Laboratories, Inc., Knoxville, Tennessee.

2-Pyridyl Amidrazone.

The reactant was synthesized following the procedure of Case (7) and obtained as white needles, m.p. 95-96° [lit. (7) m.p. 95-96°].

2,6-Pyridinediyl Diamidrazone.

This compound was prepared through a known procedure (1) as pale yellow needles, m.p. 231-232° dec.

Anal. Calcd. for C₇H₁₁N₇: C, 43.51; H, 5.74; N, 50.76. Found: C, 43.66; H, 5.72; N, 50.71.

Since the experimental procedures for the preparation of the individual groups of compounds, the 5-(*o*-aminophenyl)-1,2,4-triazoles (III and VI), the precursor amides (VII, IX, and XI), and the quinazolo[3,4-*c*]-1,2,4-triazoles (VIII, X, and XII) are very similar, the procedure for the synthesis of a representative series is presented.

3,3'-(2'',6''-Pyridinediyl)bis[5-(*o*-aminophenyl)-1,2,4-triazole] (VI).

A solution of *o*-nitrobenzoyl chloride (30.7 g., 0.17 mole) in *N,N*-dimethylacetamide (DMAC, 100 ml.) was added during 0.5 hour at 0° to 2,6-pyridinediyl diamidrazone (16.0 g., 0.083 mole) in *N,N*-dimethylacetamide (DMAC) (150 ml.) containing sodium bicarbonate (15.0 g., 0.088 mole). After complete addition, the orange reaction mixture was stirred at ambient temperature for 2 hours followed by pouring into cold water (600 ml.). The resulting yellow precipitate was washed thoroughly with water and dried over phosphorus pentoxide to yield *N,N'*-di(*o*-nitrobenzoyl)-2,6-pyridinediyl diamidrazone [(IV), 35.0 g., 81% yield] as a yellow solid, m.p. 160-162° dec. The *N*-acylamidrazone (24.6 g., 0.05 mole) was placed in *m*-cresol (300 ml.) and refluxed under argon for 5 hours followed by concentration to dryness to yield a brown residue. The brown residue was washed twice with hot methanol (250 ml.) to yield a tan insoluble solid (16.5 g., 73% crude yield), m.p. 304-308°. Recrystallization from a mixture of DMAC (130 ml.), methanol (200 ml.), and water (80 ml.) gave 3,3'-(2'',6''-pyridinediyl)bis[5-(*o*-nitrophenyl)-1,2,4-triazole] [(V), 13.0 g., 79% recovery] as tan crystals, m.p. 311-312.5° (Table I).

The nitro compound (4.6 g., 0.01 mole) and sodium sulfide nonahydrate (10.0 g., 0.04 mole) were stirred in ethylene glycol (100 ml.) to form a yellow solution which was heated to 115° under argon and stirred at 115° for 4 hours. The cooled yellow solution was diluted with water (200 ml.) and neutralized with dilute hydrochloric acid to yield a tan precipitate. The isolated dried tan solid (4.1 g., 104% crude yield) was recrystallized twice from a mixture of DMAC, methanol, and water to afford 3,3'-(2'',6''-pyridinediyl)bis[5-(*o*-aminophenyl)-1,2,4-triazole] (VI) as pale yellow granular crystals (2.0 g., 51% yield). After drying in an Abderhalden apparatus for 18 hours over phosphorus pentoxide

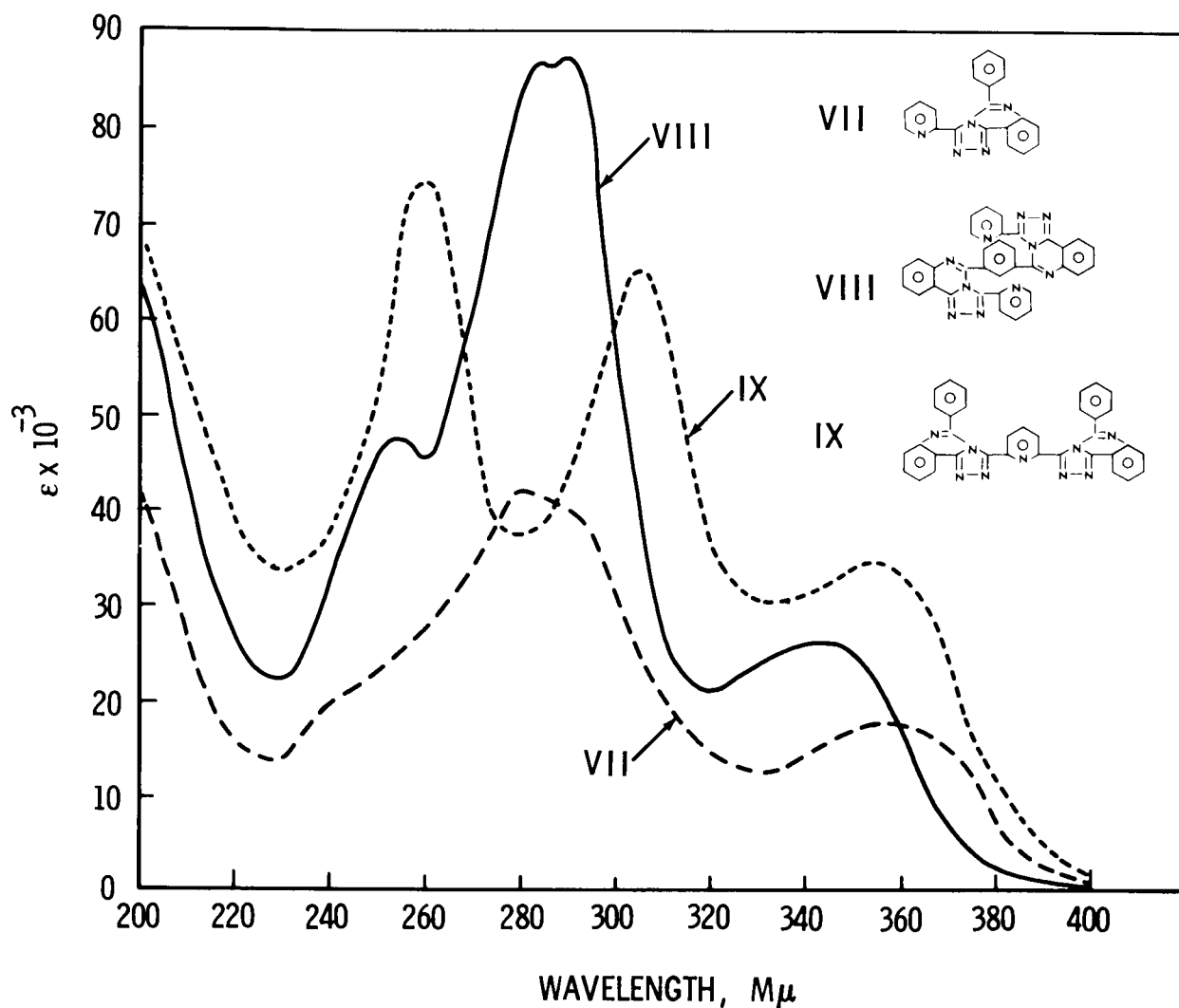


Figure 2. Ultraviolet Spectra (in sulfuric acid) of quinazolo[3,4-c]-1,2,4-triazoles.

under refluxing *m*-cresol (202°) *in vacuo*, the yellow crystals melted at 346-348° (Table I). The reduction can also be accomplished by hydrogenation in a mixture of pyridine and methanol at ambient temperature under ~ 50 psi using Adams' catalyst.

The quinazolo[3,4-c]-1,2,4-triazoles were prepared as shown in reaction schemes II and III by cyclodehydration of amide precursors, by solution condensation in polyphosphoric acid (PPA), and also by melt condensation as indicated in the following representative procedures.

3,3'-(2'',6''-Pyridinediyl)bis(5-phenylquinazolo[3,4-c]-1,2,4-triazole) *Via* Amide Precursor.

To a yellow slurry of 3,3'-(2'',6''-pyridinediyl)bis[5-(*o*-aminophenyl)-1,2,4-triazole] (1.98 g., 0.005 mole) and anhydrous sodium carbonate (1.06 g., 0.010 mole) in DMAC (50 ml.) at 0° under argon, a solution of benzoyl chloride (1.41 g., 0.010 mole) in DMAC (50 ml.) was added during 0.5 hour. The resulting almost clear orange solution was stirred at 0° for 0.5 hour followed by stirring at ambient temperature for 2 hours. Dilution with water (150 ml.) gave a yellow precipitate which was filtered, thoroughly

washed with water, and dried over phosphorus pentoxide *in vacuo*. The resulting yellow solid (2.5 g., 86% yield based upon the monohydrate), 3,3'-(2'',6''-pyridinediyl)bis[5-(*o*-benzamidophenyl)-1,2,4-triazole] hydrate (XI), melted at 202-205° dec. (Table I).

A test tube containing the yellow precursor amide under argon was introduced into a preheated oil bath at 300° and maintained at 300° for 1.0 hour. During this heating phase, the solid melted and foamed. The resulting brown product melted at 260-263°. Recrystallization from a mixture of benzene and *n*-hexane afforded near white needles of 3,3'-(2'',6''-pyridinediyl)bis[5-phenylquinazolo[3,4-c]-1,2,4-triazole], m.p. 263-264°.

Solution Condensation in PPA.

In PPA (100 g.) under argon, 3,3'-(2'',6''-pyridinediyl)bis[5-(*o*-aminophenyl)-1,2,4-triazole] (1.98 g., 0.005 mole) and benzoic acid (1.22 g., 0.01 mole) were heated to 250° during 3 hours and maintained at 250° for 0.5 hour. The partially cooled light brown solution was poured into water to precipitate a tan solid. The isolated tan solid was successively washed with aqueous sodium bicarbonate and water and dried to provide a light tan solid

(1.78 g., 77% yield), m.p. 261-263°. Recrystallization from a mixture of benzene and *n*-hexane afforded 3,3'-(2'',6''-pyridinediyl)bis(5-phenylquinazolo[3,4-*c*]-1,2,4-triazole) (XII) as white needles, m.p. 264-264.5° (Table I).

Melt Condensation.

An intimate mixture of 3,3'-(2'',6''-pyridinediyl)bis[5-(*o*-aminophenyl)-1,2,4-triazole] (1.98 g., 0.005 mole) and phenyl benzoate (1.98 g., 0.01 mole) in a test tube under argon was introduced into a preheated oil bath at 340° to form an immediate brown melt which was maintained at ~340° for 1 hour. The resulting brown foamy solid (2.11 g., 97% yield), m.p. 260-264° was recrystallized from a mixture of benzene and *n*-hexane to provide 3,3'-(2'',6''-pyridinediyl)bis(5-phenylquinazolo[3,4-*c*]-1,2,4-triazole) as fine white needles, m.p. 264-264.5°.

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