PYRIMIDINES

LV.* NEW METHOD FOR THE PREPARATION OF 1,3-DIARYLBENZO[f]QUINAZOLINES

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A new method was developed for the preparation of 1,3-diarylbenzo[f]quinazolines by condensation of β-naphthylamine, an aromatic aldehyde, and ammonia and subsequent dehydrogenation of the initially formed dihydro derivatives.

1,3-Diphenyldihydrobenzo[f]quinazoline was obtained in addition to 3-hydroxyl-1-phenylbenzo[f]quinazoline in the reaction of β-naphthylamine and dibenzalurea in acetic acid [1]. The formation of the former occurs as a result of condensation of β-naphthylamine, benzaldehyde, and the ammonia evolved during decomposition of the urea.

Little study has been devoted to the properties of arylbenzoquinazolines, but it is known that 2,4-diarylquinazolines are mild CNS depressants [2], stilbenylquinazolines are of interest as optical bleaches and scintillators [3], and that o-hydroxyarylquinazolines have photostability [4] and can be used as organic luminophores [5].

The only method for the preparation of 1,3-diarylbenzo[f]quinazolines described up until now consists in the reaction of the corresponding N-arylacylimido chlorides with aromatic nitriles in the presence of $AlCl_3$ [6]. 2,4-Diarylbenzo[h]quinazolines, for which a new method of synthesis from the lithio derivative of 1-methoxynaphthalene and aromatic nitriles was recently proposed [7], were also obtained by a similar method in [6].

Our simple method for the preparation of 1,3-diarylbenzo[f]quinazolines consists in the reaction of β-naphthylamine with aromatic aldehydes and ammonium acetate by refluxing in acetic acid. The corresponding dihydrobenzo[f]quinazolines I-VI, which do not undergo subsequent dehydrogenation under the reaction conditions, are formed in this case. We did not establish the position of the double bond in dihydro derivatives I-VI, but, in analogy with dihydroquinazolines [8], it may be assumed that the 1,2-dihydro derivative structure is more likely. The formation of dihydro derivatives is of undoubted interest, since compounds of this type have not been obtained heretofore.† They can serve as key compounds for the synthesis of various N-substituted benzo[f]quinazolines, since highly interesting preparations have recently been found precisely among N-substituted derivatives of pyrimidines [10, 11].

The formation of dihydrobenzo[f]quinazolines (I-VI) can be represented by the scheme presented on the following page.

Dihydrobenzo[f]quinazolines I-VI may be formed either as a consequence of dehydrogenation of tetrahydrobenzoquinazolines A or as a result of cyclization of unsaturated compound B [12, 13]. (See Scheme on following page).

We were unable to detect tetrahydro derivatives A in the reaction mixture, and their formation is unlikely since tetrahydropyrimidines of this type are extremely unstable [14]. The cyclization of compounds B to stabilized (by a double bond) dihydrobenzo[f]quinazoline is more likely. Any compound that contains a $>C=N$ bond, including the Schiff base of β-naphthylamine, may act as a dehydrogenating agent. For example, in the

*See [1] for communication LIV.

†The preparation of compounds that were called dihydro-6,7-benzoquinazolines (i.e., benzo[f]quinazolines) in the discussion and dihydrobenzo[f]quinazolines in the experimental section was described in [9]. Thus it is not possible to form a judgment regarding the structures of the synthesized dihydrobenzoquinazolines.

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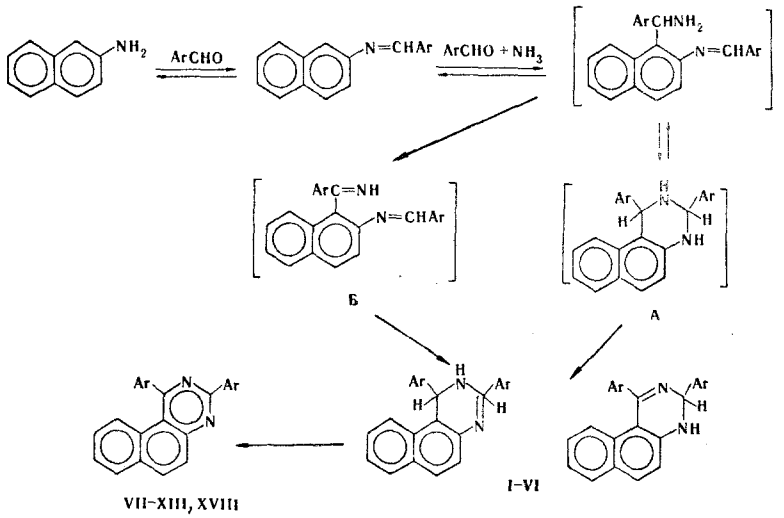

I, VII Ar = C_6H_5; II, VIII Ar = C_6H_4Cl-*p*; III, IX Ar = C_6H_4Br-*p*; IV, X Ar = $C_6H_4OCH_3$-*p*; V, XI Ar = $C_6H_4OCH_3$-*o*; VI, XII Ar = $C_6H_3(OCH_3)_2$-3,4; XIII Ar = C_6H_4OH-*p*; XVIII Ar = C_6H_4OH-*o*

preparation of benzoquinazoline VI up to 20% N-(3,4-dimethoxybenzyl)-β-naphthylamine (XIV) was isolated in individual experiments.

When the dihydrobenzoquinazolines are refluxed with acetic anhydride, they form N-acetyl derivatives. We did not establish the position of the acetyl group, but the chromatographic behavior and the data from the PMR spectrum of the acetyl derivative (XV) make it possible to assume that only one isomer is formed.

The subsequent dehydrogenation of dihydrobenzoquinazolines I-VI proceeds with difficulty. Negative results were obtained when they were refluxed with chloranil in xylene and when an attempt was made to dehydrogenate them by the bromination–dehydrobromination method. We were able to aromatize quinazolines I-VI by heating with sulfur at high temperatures. The yields are higher in the case of benzoquinazolines XII, X, and XIII, and side products are detected in the reaction mixture in the case of the reaction of halo derivatives II and III and o-methoxy derivative V with sulfur. The determination of the molecular weights of the products isolated by chromatography on silica gel by mass spectrometry provides a basis for the assumption that the halogen in one aromatic ring is replaced by an SH group and that a mixture of XI and 1,3-(o-hydroxyphenyl-, o-methoxyphenyl) benzo[f]quinazoline (XVII) is formed in the dehydrogenation of methoxybenzoquinazoline V.

It is interesting to note that the IR spectra of I-VI contain a band of medium intensity at ~1300 cm^{-1}, which vanishes in the case of dehydrogenation, and an intense band at 1380-1390 cm^{-1}, which is evidently one of the characteristic bands of stretching vibrations of the pyrimidine ring [15], appears in place of it in the spectra of VII-XIII, XVII, and XVIII.

The corresponding p- and o-hydroxyphenylbenzo[f]quinazolines XIII and XVIII were obtained by refluxing p- and o-methoxyphenylbenzoquinazolines X and XI with concentrated HBr in acetic anhydride.

The structures of all of the compounds obtained in this research were confirmed by spectral methods, mass spectrometric determination of the molecular weights, and the results of elementary analysis.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of alcohol solutions of the compounds were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a Varian A56/60A spectrometer with hexamethyldisiloxane as the internal standard. The molecular weights were determined with MS-902 and MC-3301 mass spectrometers with a system for the direct introduction of the samples at 120-140°C.

1,3-Diaryldihydrobenzo[f]quinazolines. A mixture of 0.05 mole of β-naphthylamine, 0.1 mole of aromatic aldehyde, 0.2 mole of anhydrous CH_3COONH_4, and 30 ml of glacial CH_3COOH was refluxed at 135°C for 5 h, after which the resulting solution was cooled and poured into 300 ml of water. The aqueous mixture was neutralized with solid $NaHCO_3$ and extracted with four 80-ml portions of $CHCl_3$. The chloroform extracts were washed with

TABLE 1. 1,3-Diaryldihydrobenzo[f]quinazolines

Compound	mp, °C	M	Found, % C	H	N	Empirical formula	Calc., % C	H	N	λ_{max}, nm (lg ε)	ν_{NH}, cm^{-1} (KBr)	Yield, %
I	219—220	334	86,2	5,6	8,3	$C_{24}H_{18}N_2$	86,2	5,4	8,4	204 (4,72), 239 (4,68), 278 (4,33), 287 (4,28), 345 (4,22)	3400	51
II	212—214	—	71,7	3,9	7,1	$C_{24}H_{16}Cl_2N_2$	71,5	4,0	6,9	208 (4,58), 234 (4,58), 278 (4,18), 290 (4,08), 353 (3,92)	3420	25
III	232—237	492	58,5	3,1	5,6	$C_{24}H_{16}Br_2N_2$	58,5	3,3	5,7	210 (4,60), 228 (4,60), 278 (4,25), 290 (4,11), 358 (3,90)	3320	34
IV	229—230	394	78,8	5,7	7,4	$C_{26}H_{22}N_2O_2$	79,2	5,6	7,1	208 (4,73), 220 (4,68), **255 (4,38)**, 278 (4,51), **340 (4,00)**	3400	30
V	204—206	—	79,2	5,5	7,3	$C_{26}H_{22}N_2O_2$	79,2	5,6	7,1	**220 (4,71)**, 225 (4,35), **282 (4,37)**, 334 (3,88)	3420	64
VI	110—113[a]	454	74,2	5,7	6,0	$C_{28}H_{26}N_2O_2$	74,1	5,7	6,2	**208 (4,49)**, 228 (4,50), **250 (4,16)**, 278 (4,25), 290 (4,22), 345 (3,86)	3400	54

[a]From benzene–petroleum ether; the remaining compounds were crystallized from alcohol.

TABLE 2. 1,3-Diarylbenzo[f]quinazolines

Compound	mp, °C	M	Found, % C	H	N	Empirical formula	Calc., % C	H	N	λ_{max}, nm (lg ε)	Yield, %
VII	152—154[a]	332	—	—	—	—	—	—	—	216 (4,59), 261 (4,53), 284 (4,72)	85
VIII	184—186	—	71,6	3,4	7,0	$C_{24}H_{14}Cl_2N_2$	71,8	3,4	6,9	205 (4,48), 221 (4,54), 265 (4,43), 288 (4,65)	36 40[b]
IX	179—182	488	58,4	2,9	5,6	$C_{24}H_{14}Br_2N_2$	58,7	2,9	5,7	207 (4,53), 221 (4,58), 267 (4,51), 291 (4,74)	
X	166—167	—	79,6	5,2	7,3	$C_{26}H_{20}N_2O_2$	79,5	5,1	7,1	205 (4,47), 226 (4,44), 270 (4,11), 301 (4,56)	84
XI	213—216[c]	392	79,5	5,1	7,1	$C_{26}H_{20}N_2O_2$	79,5	5,1	7,1	206 (4,61), 218 (4,63), 271 (4,52), 301 (4,30)	—
XII	195—198[c]	452	73,9	5,5	6,2	$C_{28}H_{24}N_2O_4$	74,3	5,3	6,2	208 (4,66), 226 (4,58), 307 (4,56)	80
XIII	341—345	364	78,4	4,7	7,6	$C_{24}H_{16}N_2O_2$	79,0	4,4	7,7	206 (4,48), 228 (4,55), 303 (4,67)	98
XVII	181—183[c]	378	79,3	5,0	7,4	$C_{25}H_{18}N_2O_2$	79,4	4,8	7,4	205 (4,63), 220 (4,63), 283 (4,64), 323 (4,30)	—
XVIII	183—185[c]	d	78,7	4,5	—	$C_{24}H_{16}N_2O_2$	79,0	4,4	—	208 (4,56), 222 (4,58), 286 (4,60), 333 (4,24)	70

[a]This compound had mp 153°C [2]. [b]This is the yield with respect to the dehydrogenation reaction. [c]From xylene; the remaining compounds were crystallized from alcohol. [d]Found: M 364 and 1211. Calculated: M 364 and 1230.

a 10% solution of $NaHCO_3$ and water, dried with $MgSO_4$, and evaporated. The oily residue was triturated thoroughly with ether to give dihydrobenzoquinazolines I, II, and IV. Quinazoline V precipitated when the acetic acid solution was neutralized, and was removed by filtration and washed thoroughly with ether. The physical constants and yields of I, II, IV, and V are presented in Table 1.

PMR spectrum of I (d_6-DMSO), δ: 6.50 (s, 1H, C–H) and 7.30-7.99 ppm (m, 16H, aromatic protons).

1,3-Bis(p-bromophenyl)dihydrobenzo[f]quinazoline (III) and 1,3-Bis(p-bromophenyl)benzo[f]quinazoline (IX). The reaction and workup of the reaction mixture were carried out as in the preceding experiment. The oil that remained after evaporation of the chloroform extracts was triturated with ether, and the precipitate that formed in 1 week was removed by filtration and worked up to give III. The filtrate was evaporated, and the residue was subjected to thin-layer chromatography (TLC) on silica gel [$CHCl_3$–benzene–alcohol (20:20:1), R_f 0.33] to give an additional amount of III (Table 1) and 0.1 g of IX with R_f 0.76 (Table 2).

1,3-Bis(3,4-dimethoxyphenyl)dihydrobenzo[f]quinazoline (VI) and N-(3,4-Dimethoxybenzyl)-β-naphthylamine (XIV). The reaction was carried out as in the preceding experiment, and the resulting solution was cooled and allowed to stand for 12-15 h in a refrigerator. The precipitate was removed by filtration and washed with a 10% solution of $NaHCO_3$ and water to give 14-20% XIV with mp 145-147°C (alcohol). IR spectrum: 3340 cm^{-1} (N–H). UV spectrum, λ_{max}(log ε): 208 (4.54), 215 (4.49), 248 (4.71), 286 (4.14), 294 (4.05), and 336 nm (3.51). PMR spectrum ($CDCl_3$), δ: 3.92 (s, 6H, OCH_3), 4.46 (s, 2H, CH_2), and 6.94-7.95 ppm (m, 10H, aromatic protons). Found: C 78.2; H 6.6; N 4.9%; M 293. $C_{19}H_{19}NO_2$. Calculated: C 77.9; H 6.5; N 4.8%; M 293.

The filtrate from the separation of XIV was poured into 200 ml of water, and the aqueous mixture was neutralized with dry $NaHCO_3$ and allowed to stand for 15 h. The resulting precipitate was removed by filtration and dissolved in the minimum amount of alcohol. The solution was treated with water to precipitate VI (Table 1).

N-Acetyl-1,3-bis(3,4-dimethoxyphenyl)dihydrobenzo[f]quinazoline (XVI). The aqueous alcohol filtrate from the preceding experiment (after separation of VI) was evaporated, and the residue was refluxed with 20 ml of acetic anhydride for 3 h. The solution was cooled and poured into 150 ml of water, and the aqueous mixture was made alkaline to pH 8.5. The precipitate was removed by filtration and washed with water to give 0.8 g of XVI with mp 158-165°C (alcohol). IR spectrum: 1260 (C–O) and 1680 cm^{-1} (amide C=O). Found: C 72.6; H 5.5; N 5.9%. $C_{30}H_{28}N_2O_5$. Calculated: C 72.5; H 5.7; N 5.7%.

N-Acetyl-1,3-diphenyldihydrobenzo[f]quinazoline (XV). A solution of 2 g (6 mmole) of I in 5 ml of of acetic anhydride was refluxed for 5 h, after which it was cooled and allowed to stand for 12-15 h in a refrigerator. The resulting precipitate was removed by filtration and washed with water and ether to give 0.9 g (40%) of XV with mp 158-160°C (alcohol) and R_f 0.71 [on Silufol UV-254 plates with a $CHCl_3$–benzene–alcohol system (20:20:1)]. IR spectrum: 1690 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 210 inflection (4.48), 225 (4.67), 253 (4.36), 278 (4.49), 288 (4.43), and 345 nm (4.20). PMR spectrum (d_6-DMSO), δ: 1.73 (s, 3H, CH_3) and 7.10-8.08 ppm (m, 17H, aromatic and C–H protons). Found: C 83.2; H 5.3; N 7.6%. $C_{26}H_{20}N_2O$. Calculated: C 83.0; H 5.3; N 7.4%.

1,3-Diarylbenzo[f]quinazolines (VII-X and XII). A) Molar amounts of 1,3-diaryldihydrobenzo[f]quinazoline and sulfur were mixed thoroughly, and the mixture was heated at 220-260°C for 45 min. The melt was then cooled and triturated with alcohol, and the solid material was removed by filtration to give quinazolines VII, VIII, X, and XII. Benzoquinazoline IX was extracted from the melt with hot alcohol and had mp 179-185°C and R_f 0.62 [chloroform–benzene (1:1), silufol UV-254 plates]. The physical constants and yields of VII-X and XII are presented in Table 2.

The alcohol-insoluble portion (after extraction of IX) was dissolved in dimethylformamide (DMF) and precipitated by the addition of water (this procedure was carried out twice). The product (in 25% yield) was 1,3-(p-bromophenyl-, p-mercaptophenyl)benzo[f]quinazoline with mp > 300°C and R_f 0.77 [chloroform–benzene (1:1)]. A molecular weight of 442.0132 was found by high-resolution mass spectrometry. The empirical formula $C_{24}H_{15}BrN_2S$ was calculated from this molecular weight.

B) A solution of 0.046 g (0.29 mmole) of $KMnO_4$ in 0.8 ml of water was added in the course of 5 min at room temperature to a solution of 0.20 g (0.4 mmole) of III in 10 ml of dioxane, and the mixture was allowed to stand for 1 h. The small excess amount of $KMnO_4$ was decomposed by the addition of a few drops of concentrated HCOOH, the mixture was filtered, and the dioxane was removed by vacuum evaporation. The residual oil crystallized on standing to give 0.1 g (50%) of IX, the IR spectrum of which coincided completely with the IR spectrum of IX obtained by method A.

1,3-Bis(o-methoxyphenyl)benzo[f]quinazoline (XI) and 1,3-Bis(o-hydroxyphenyl-, o-methoxyphenylbenzo[f]quinazoline (XVII). A mixture of 1.5 g (3.8 mmole) of V and 0.12 g (3.8 mmole) of sulfur was heated at 220-260°C for 45 min, after which it was cooled and triturated with ether. The ether mixture was filtered to give 0.9 g of a mixture of XI and XVII (mp 188-200°C), which was separated into its individual components by fractional crystallization from xylene with monitoring of the purity by TLC on silica gel with a $CHCl_3$–benzene–alcohol system (20:20:1). Workup gave 0.6 g of XI with R_f 0.49 and 0.2 g of XVII with R_f 0.63.

1,3-Bis(p-hydroxyphenyl)benzo[f]quinazoline (XIII). A 3.5-ml sample of acetic anhydride was added to a suspension of 1.9 g (4.8 mmole) of X in 7 ml of concentrated HBr, and the mixture was refluxed for 7 h. Another 1 ml of HBr and 1 ml of glacial acetic acid were added to the mixture, and it was refluxed for another 7 h. The resulting suspension was cooled, and the bright-yellow precipitate of XIII was removed by filtration and washed thoroughly with a 10% solution of $NaHCO_3$ and water. The filtrate was poured into water, and the pre-

cipitated XIII was removed by filtration and washed with 10% $NaHCO_3$ solution and water. The overall yield of XIII was 1.7 g (Table 2). PMR spectrum (d_6-DMSO), δ: 9.86 (OH, 2H) and 6.94-8.44 ppm (aromatic protons, 14H).

1,3-Bis(o-hydroxyphenyl)benzo[f]quinazoline (XVIII). A 3.2 ml sample of concentrated HBr and 1.54 ml of acetic anhydride were added to 1 g of a mixture of products XI and XVII, and the mixture was refluxed for 20 h; 3.2 ml of HBr and 1.5 ml of acetic anhydride were added to the reaction mixture every 8 h. The mixture was then cooled and poured into 3.2 ml of HBr, and the precipitated hydrobromide of XVIII, with mp 225-235°C (from acetic acid, mp 225-230°C), was removed by filtration. The hydrobromide was heated with stirring with 50 ml of 10% $NaHCO_3$ solution at 75-80°C for 2 h, and the precipitated XVIII was removed by filtration and washed with water. The yield was 0.7 g.

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