SYNTHESIS OF BENZO[g]QUINOLINE DERIVATIVES

IV. Formation of 4-Amino-Substituted Benzo[g]quinolines*

A. F. Bekhli and N. P. Kozyreva

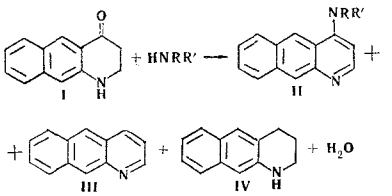
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 2, pp. 294–296, 1969

UDC 547.836.07:543.422.6

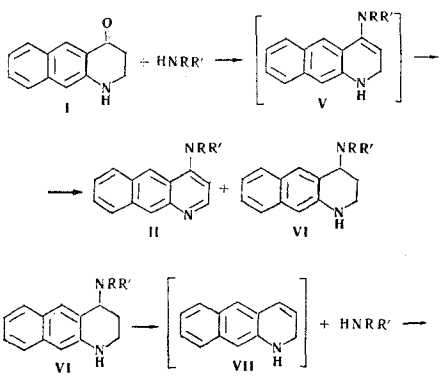
4-Amino-substituted benzo[g]quinolines have been synthesized for the first time by the condensation of 4-oxo-1,2,3,4-tetrahydrobenzo[g]-quinoline with amines. This reaction is characterized by the addition of the amine, the splitting out of water, and the complete aromatization of the initial hydrogenated heterocyclic system. The UV spectra of the compounds obtained are similar to those of 4-amino-substituted quinolines, their maxima being displaced somewhat into the long-wave region.

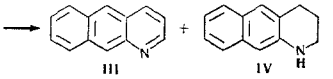
4-Amino-substituted benzo[g]quinolines (II) have not previously been described because of the absence of methods for their synthesis. Nevertheless, this series of compounds, because of its structural analogy with the therapeutically valuable derivatives of 4-aminoquinoline and 9-aminoacridine is of undoubted interest in the search for biologically-active compounds.

We have found a method consisting in the condensation of 4-oxo-1,2,3,4-tetrahydrobenzo[g]quinoline (I) with amines, which leads directly to the corresponding compounds II [1]. The reaction is accompanied by the splitting out of water and the formation of products having no substituent in position 4: benzo[g]quinoline (III) and 1,2,3,4-tetrahydrobenzo[g]quinoline (IV).



We have discussed this reaction previously for the case of the condensation of I with ammonia [2], a mechanism being proposed for the formation of III and IV. According to this, the transformations taking place here can be represented by the following scheme:





The intermediate reaction product—a 4-amino-1,2-dihydrobenzo[g]quinoline (V)—disproportionates to form the corresponding compound II and its tetrahydro derivative (VI) which then decomposes with the liberation of the amine and the formation of III and IV.

Forcing the reaction in the direction of the predominant formation of II, and not its analogs hydrogenated in the pyridine ring, is achieved by creating conditions preventing the disproportionation of V and favoring its oxidation. It has been shown that the use of an oxidizing agent (o-nitrophenol) increases the yield of II (c,d) from 39.1 to 62.0%.

In order to demonstrate the formation of the aromatized compounds in this reaction (method A), one of the derivatives (IId) was obtained by another route (method B) from 4-chlorobenzo[g]quinoline [3]. The two products obtained by different methods proved to be completely identical.

Since the reaction described begins as the nucleophilic attack of the carbonyl carbon by the amine, the basicity of the reacting amine and the steric hindrance created by the features of its structure exert an influence on the course of the reaction. With fairly basic amines (pK_a ~ 5 and above), compounds II are formed with yields of 60–70%; with weakly basic amines (p-nitroaniline; pK_a 1.1) the yield of compounds II is only 19%; and with still less basic amines (2-chloro-4-nitroaniline) the reaction does not take place at all. The reaction does not take place, either, with such branched secondary amines as diethanolamine and dibutylamine [diisobutylamine], while with cyclic amines (cyclohexylamine, N-methylpiperazine) creating no steric hindrance, compounds II are formed with good yields (up to 75%).

The IR spectra of the compounds synthesized have bands characteristic for the stretching vibrations of an NH group (table).

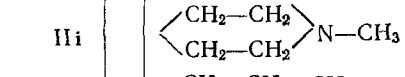
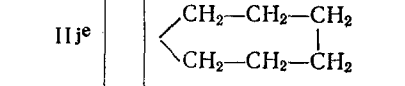
From the data on the UV spectra (table) it can be seen that compounds II have two main maxima at ~250 and ~400 nm. The spectra are similar to that of unsubstituted 4-aminobenzo[g]quinoline [2] and to those of the corresponding substituted 4-aminoquinolines [4], differing from the latter by a displacement of the maxima in the long-wave direction.

EXPERIMENTAL

4-Amino-substituted benzo[g]quinolines (II). Method A. A mixture of 0.05 mole of I, 0.1 mole of an amine, and 0.015 mole of o-

*For part III, see [2].

4-Amino-Substituted Benzo[g]quinolines

Compound	R	R′	Mp, °C (solvent for crystallization)	λ_{max}, nm	log ε	ν_{N-H}, cm^{-1}	Empirical formula	Found, %			Calculated, %			Yield, %
								C	H	N	C	H	N	
IIa	H	$(CH_2)_3CH_3$	137—138 (aqueous ethanol)	243; 252—254; 302—306; 390	4.73; 4.67; 3.52; 3.96	3230 m	$C_{17}H_{18}N_2$	81.48	7.34	11.14	81.56	7.24	11.19	60.2
IIb[a]	H	$CH(CH_3)(CH_2)_3N(C_2H_5)_2$	134—135 (heptane)	243; 254; 302—306; 390	4.72; 4.69; 3.50; 3.92	3250 m	$C_{22}H_{29}N_3$	79.00	8.61	12.49	78.76	8.71	12.53	74.4[a]
IIc	H	C_6H_5	247—248 (aqueous ethanol)	252—254; 320; 395—397	4.76; 3.60; 4.05	3240 w., broad	$C_{19}H_{14}N_2$	84.63	5.66	10.39	84.41	5.22	10.32	58.7 39.4[b]
IId[c]	H	p-$CH_3OC_6H_4$	205—206 (aqueous ethanol)	248; 395—400	4.83; 4.06	3240 W. broad	$C_{20}H_{16}N_2O$	79.97	5.38	9.43	79.98	5.37	9.33	62.0 39.1[b]
IIe[d]	H	p-$C_2H_5OC_6H_4$	215—216 (ethanol)	246—248; 400—405	4.84; 4.09	3170 m., broad	$C_{21}H_{18}N_2O$	80.04	5.72	9.20	80.23	5.77	8.91	62.4
IIf	H	p-HOC_6H_4	274—276 (reprecipitation)	246—250; 400—405	4.80; 4.04	3270 m	$C_{19}H_{14}N_2O$	—	—	9.24	—	—	9.79	54.7
IIg	H	3-$N(C_2H_5)_2CH_2$-4-HOC_6H_3	207—207.5 (decomp., aqueous acetone)	248; 395	4.76; 4.01		$C_{24}H_{25}N_3O$	77.68	6.84	10.98	77.59	6.78	11.31	45.3
IIh	H	p-$NO_2C_6H_4$	202—203	256—258; 360; 405—410	4.47; 3.83; 4.12		$C_{19}H_{13}N_3O_2$	—	—	12.97	—	—	13.32	19.0
IIi			140—142[d]	254; 324—326; 360; 375	4.88; 3.43; 3.73; 3.81		$C_{18}H_{19}N_3$	77.41	6.96	15.24	77.94	6.90	15.15	38.2
IIj[e]														
		salicylate	190—191 (decomp.)	248; 306—308; 415	4.71; 3.86 3.95		$C_{19}H_{20}N_2 \cdot C_7H_6O_3$	75.09	6.05	6.95	75.16	6.31	6.76	

[a]Diphosphate: mp 222–223° C. Found, %: N 7.94. Calculated for $C_{22}H_{29}N_2 \cdot 2H_3PO_4$, %: N 7.91. [b]Yield on performing the reaction without an oxidizing agent. [c]Hydrochloride: mp 260–262° C. Found, %: Cl 10.51. Calculated for $C_{20}H_{16}N_2O \cdot HCl$, %: Cl 10.53. [d]Hydrochloride: mp 266–267.5° C. Found, %: Cl 10.22. Calculated for $C_{21}H_{18}N_2O \cdot HCl$, %: Cl 10.11. [e]Base—an oil. Yield 75.7%. The data for the salicylate are given in the table.

nitrophenol was heated in isoamyl alcohol (25 ml) at 160–180° C for 1–2.5 hr with stirring, the water formed being distilled off azeotropically. After cooling, the reaction mixture was poured into 10% caustic soda solution and the product was extracted with benzene or filtered off. The compounds were purified by reprecipitation and crystallization. With the exception of **IIj**, compounds **II** (table) consisted of yellow to orange (**IIh**) crystalline substances soluble in the majority of organic solvents (with the exception of **IIf**) and insoluble in water. The solutions have a blue-violet fluorescence. As a by-product, a small amount of **III** was isolated in the form of the picrate with mp 256–257° C.

Method B. A mixture of 0.5 g (0.002 mole) of 4-chlorobenzo[g]-quinoline [3] and 0.3 g (0.002 mole) of p-anisidine was heated in 2.5 g of phenol at 170° C with stirring for 2 hr. The reaction mixture was poured into 10% caustic soda solution and the product was filtered off and washed with water. After purification by recrystallization and precipitation, the yield of **IId** was 0.4 g (56.9%), mp 205–206° C (aqueous ethanol), giving no depression of the melting point in admixture with a sample of the **IId** obtained by method A.

4-(3'-Diethylaminomethyl-4'-hydroxyphenyl)aminobenzo[g]-quinoline (IIg). A mixture of 10.2 g (0.0355 mole) of **IIf**, 3.3 g (0.0355 mole) of 32% formaldehyde solution, 6.6 g (0.09 mole) of diethylamine, and 90 ml of ethanol was boiled for 9 hr. The volatile products were distilled off in vacuum, the residue was dissolved in dilute HCl, the solution was treated with activated carbon, and the product was precipitated with ammonia. This gave 6.0 g (45.3%) of **IIg** (table). The UV spectra were taken on an SF-4 spectrophotometer in 95% ethanol and the UR spectra on a UR-10 spectrophotometer in the form of tablets with KBr in the case of **IIa, b, e,** and **f** and in paraffin oil in the case of **IIc** and **d**.

REFERENCES

1. A. F. Bekhli, DAN, **101**, 679, 1955.

2. A. F. Bekhli and N. P. Kozyreva, KhGS [Chemistry of Heterocyclic Compounds], **4**, 307, 1968.

3. A. F. Bekhli and N. P. Kozyreva, KhGS [Chemistry of Heterocyclic Compounds], **4**, 304, 1968.

4. J. M. Hearn, R. A. Morton, and J. C. E. Simpson, J. Chem. Soc., 3319, 1951.

1 November 1966

Martsinovskii Institute of Medicinal Parasitology and Tropical Medicine, Moscow