STUDIES IN THE SYNTHESIS OF 5,6-BENZOQUINOLINES

I. 2-Aryl-5,6-benzolepidines

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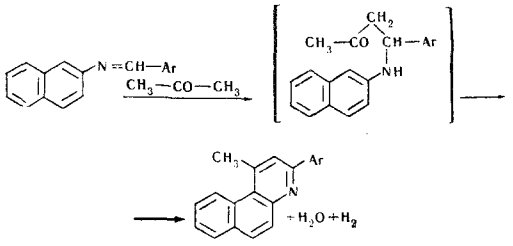
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 5, pp. 866–868, 1968

UDC 547.831.2'832.5.07:543.422.4

2-Phenyl-5,6-benzolepidines were synthesized by the condensation of arylidene-2-naphthylamines with acetone in the presence of hydrochloric acid. The influence of various substitutents in the aromatic aldehydes on the course of the reaction was studied. It was shown that the introduction of certain substituents, e.g. a nitro or methyl group into the ortho-position of the azomethine residue caused an appreciable lowering in the yield of arylbenzolepidine. A cyclic product could not be obtained when the aldehyde residue contained two methyl groups in the ortho-position. The reaction of 2,4,6-trimethylbenzylidene-2-naphthylamine with acetone under severe conditions afforded the adduct β-mesityl-β-(2-naphthylamino)butanone.

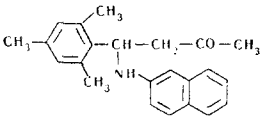
In previous papers [1, 2], it was shown that catalytic condensation of azomethines formed from 2-naphthylamine and aromatic aldehydes with carbonyl compounds containing methyl groups in the alpha-position to the carbonyl group afforded 2-phenyl-5,6-benzoquinoline. We consider that the condensation of azomethines with acetone, which enables 2-aryl-5,6-benzolepidines, compounds very difficult of access, to be obtained in a relatively simple manner, was a reaction of definite interest.



However, this reaction has been inadequately studied by previous workers.

Continuing our studies in this field, we condensed with acetone arylidene-2-naphthylamines prepared from aromatic aldehydes containing substituents of different types. The influence of the various substitutents was determined by the yield of the product. The experimental data indicate that the most favorable influence on the yield of the required product is achieved by groups which lower the electron-density on the hydrogen atom of the azomethine bond. This effect increases the electrophilic character of this atom and nucleophilic addition of acetone to the azomethine bond is facilitated.

An arylidene-2-naphthylamine with an ortho-substituent in the aryl residue was condensed with acetone to evaluate the influence of steric factors. It could be assumed that these substitutents exert steric hindrance which obstructs access to the reaction center. Ortho-substituents such as fluorine or hydroxyl, which have relatively small volumes, cannot exert any appreciable hindrance whatever. Condensation of these azomethines with acetone proceeds readily with fair yields. The introduction of a nitro-group into the ortho-position of the aryl residue significantly lowers the yield of the desired product, although the electronic effect of this substituent favorably influences the course of the required reaction. Evidently the substituting group here is already exerting a steric influence. There is even more distinct evidence of the influence of steric factors with o-methyl-substituted aldehydes. We studied the reaction of acetone with azomethines formed from p-tolualdehyde, 2,4-dimethylbenzaldehyde and 2,4,6-trimethylbenzaldehyde. 2-(4'-Methylphenyl)-5,6-benzolepidine was obtained with a 34% yield. Under the same conditions 2,4-dimethylbenzylidene-2-naphthylamine gave only 20% of 2-(2',4'-dimethylphenyl)-5,6-benzolepidine. Finally, an azomethine with two methyl groups in the o-position of the aryl residue—2,4,6-trimethylbenzylidene-2-napthylamine—would not be cyclized at all. Prolonged action under fairly drastic conditions afforded the addition product of acetone to the azomethine bond—β-mesityl-β-(2-naphthylamino)butanone (1).



It is important to note that all previous attempts to isolate the acetone—arylidene-2-naphthylamine adduct formed in the presence of acid catalysts were unsuccessful as a rule. This is undubtedly explained by the high reactivity of the intermediate compounds, which readily cyclized to form 5,6-benzoquinoline derivitives. Obviously, the presence in the adduct I of substitutents which cause steric hindrance changes the spatial position of the side chain as a result of which its carbonyl group is significantly separated from the α-carbon atom of the naphthalene nucleus and cyclization becomes impossible.

The composition and structure of the compounds synthesized were confirmed by empirical analysis and IR spectroscopy. The arylbenzolepidine spectra do not contain characteristic absorption bands for C=O and N—N stretching vibrations. However, there was a strong band at 1670 cm^{-1} and a band of medium intensity with a frequency of 3310 cm^{-1}.

2-Aryl-5,6-benzolepidines

No.	Compound	Mp, °C	Empirical formula	N, % found	N, % calculated	Yield %
1	2-(4′-Chlorophenyl)-5,6-benzolepidine	172	$C_{20}H_{14}ClN$	4.69 4.80	4.62	.51
2	2-(3′-Chlorophenyl)-5,6-benzolepidine	159	$C_{20}H_{14}ClN$	4.73 4.78	4.62	57
3	2-(4′-Bromophenyl)-5,6-benzolepidine	174	$C_{20}H_{14}BrN$	3.97 4.11	4.00	48
4	2-(4′-Fluorophenyl)-5,6-benzolepidine	126	$C_{20}H_{14}FN$	4.94 5.02	4.87	46
5	2-(2′-Fluorophenyl)-5,6-benzolepidine	119	$C_{20}H_{14}FN$	4.89 4.99	4.87	39
6	2-(3′-Fluorophenyl)-5,6-benzolepidine	141	$C_{20}H_{14}FN$	4.93 5.06	4.87	53
7	2-(2′-Hydroxyphenyl)-5,6-benzolepidine	151	$C_{20}H_{15}NO$	5.03 5.15	4.91	64
8	2-(4′-Hydroxyphenyl)-5,6-benzolepidine	241 242	$C_{20}H_{15}NO$	4.89 5.12	4.91	30
9	2-(3′-Hydroxyphenyl)-5,6-benzolepidine	214	$C_{20}H_{15}NO$	5.07 5.15	4.91	44
10	2-(3′,4′-Dimethoxyphenyl)-5,6-benzolepidine	132	$C_{22}H_{19}NO_2$	4.33 4.40	4.25	41
11	2-(3′-Methoxy-4′-hydroxyphenyl)-5,6-benzolepidine	212	$C_{21}H_{17}NO_2$	4.58 4.61	4.44	38
12	2-(2′-Hydroxy-3′-methoxyphenyl)-5,6-benzolepidine	171	$C_{21}H_{17}NO_2$	4.49 4.57	4.44	50
13	2-(4′-Ethoxyphenyl)-5,6-benzolepidine	157	$C_{22}H_{19}NO$	4.55 4.63	4.47	36
14	2-(2′-Methyl-4′-methoxyphenyl)-5,6-benzolepidine	111	$C_{22}H_{19}NO$	4.60 4.66	4.47	18
15	2-(2′-Nitrophenyl)-5,6-benzolepidine	180	$C_{20}H_{14}N_2O_2$	9.05 9.11	8.92	27
16	2-(4′-Methoxyphenyl)-5,6-benzolepidine	152	$C_{21}H_{17}N$	4.99 5.08	4.97	34
17	2-(2′,4′-Dimethylphenyl)-5,6-benzolepidine	150	$C_{22}H_{19}N$	4.87 4.90	4.71	20

EXPERIMENTAL

General synthetic method for 2-aryl-5,6-benzolepidines. Equimolar amounts of aldehyde and 2-naphthylamine were mixed in a three-necked flask, fitted with a stirrer, reflux condenser and dropping funnel. Ethanol was added and the mixture heated in a boiling water bath with vigorous stirring. After 20–30 min, acetone (an approximately three-fold excess with respect to the calculated quantity), HCl (in a proportion of 1–2 g of conc. HCl per 0.01 mole of azomethine) and an equimolar quantity of nitrobenzene were added from the funnel. Heating was continued for a further 30–90 min, depending on the activity of the azomethine. The reaction mixture was cooled, and the precipitate of arylbenzolepidine (that had deposited) was filtered off and was washed on the filter with ammonia solution, water, and cold methanol. It was dried and recrystallized from benzene-ethanol or from ethanol.

The products synthesized were crystalline substances, readily soluble in aromatic hydrocarbons, dioxane, and dimethylformamide, more sparingly in ethanol and chloroform. The experimental results and analytical data are shown in the table.

Condensation of 2,4,6-trimethylbenzylidene-2-naphthylamine with acetone. 5.5 g of azomethine (0.02 mole), 3 ml of acetone, 2 ml of conc. HCl and 10 ml of ethanol were heated in a sealed tube at 100° C for 1 hr. The temperature was gradually increased to 130–140° and maintained at the latter for a further 2 hr. After cooling, the tube was opened and the contents transferred to a beaker; 20–30 ml of methanol was added to separate the crystalline precipitate from the viscous resinous mass. The precipitate was filtered off, treated with conc. ammonia solution, washed with water and methanol, and dried. Yield 2.2 g. (36%) of I. After crystallizing from aqueous dimethylformamide, mp 247°. Found, %: C 83.20, 83.31; H 7.38, 7.46; N 4.29, 4.40. Calculated for $C_{23}H_{25}NO$, %: C 83.38; H 7.55; N 4.23. IR spectra ν CM^{-1}: 739(s), 749(s), 808(s), 854(s), 1390(s), 148(s), 1520(m), 1610(m), 1670(s), 2920(m), 3050(m), 3310(m).

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14 July 1966 Perm State Pedagogic Institute