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Invited Lecture

The Synthesis of Some Condensed Heterocyclic Compounds*

M. Jančevska-Nikolovska

Faculty of Chemistry, University »Kiril i Metodij«, 91000 Skopje, Yugoslavia

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In continuation of investigations in the field of heterocyclic compounds, it was of interest to synthesize the condensed heterocyclic compounds with n-hexyl group used as substituent.

For this aim, reactions were carried out with n-hexylbenzene and different reactants at different reaction conditions and by this, through the intermediates were obtained appropriate condensed heterocyclic compounds.

The reaction capabilities of the characteristic functional groups in these compounds were investigated by different reactions.

The synthesized condensed heterocyclic compounds and their derivatives were identified by elemental microanalysis and IR spectra.

Heterocyclic condensed nitrogen compounds, because of their physiological action, are the subject of many scientific investigations and they have a very important place in chemical cancerology ever since Barry et al.[1,2] found that dibenzoacridine is a weak cancerogen. Buu-Hoî and their collaborators have synthesized a whole series of compounds of this type in which they investigated the bonds between their molecular structure and possible oncological action. Their biological investigations have established that cancerogenic characteristics can vary in accordance with the relative position of their nuclei and of the substituents in relation to the heteroatom[3—9].

Carrying them in more heteroatoms, *i. e.* nitrogen atoms, polycyclic molecules have stronger cancerogenic action. On the other hand, heterocyclic condensed molecules can lose their cancerogenic characteristics if they are partially hydrogenated. They are even used as inhibitors of strongly cancerogenic molecules, which represents a very important phenomenon for scientific investigations in wider areas[3,10].

Taking into consideration Bernthsen's statement[11] that the methyl radical in the para position against the heteroatom increases the cancerogenic activity in benzoacridine, and using the modified method of Buu-Hoï, Knoevenagel and Lecocq[12—14], it was of interest to synthesize and examine the onco-

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logical action of the benzoacridines in the para position against the heteroatom. They have substituents with more carbon atoms (methyl, ethyl, etc.).

Also, a great number of substituted isatins and their derivatives find their application because of their anesthetical, antibacteriological and tuberculostatic action. It is thus a matter of scientific and economic interest to achieve a synthesis of these compounds and to begin a study of their characteristics.

Classical and modified methods were applied for the synthesis of these compounds.

In the starting reactions we used 4-(n-hexyl)acetophenon[15] obtained by the Friedel-Crafts reaction from n-hexylbenzene and acetylchoride in the presence of anhydrous methylene chloride. The oxime of 4-(n-hexyl)acetophenone was obtained refluxing the ketone with $NH_2OH.HCl$ in the ratio 1:2 for two hours in the presence of CH_3COONa and excess of ethanol medium.

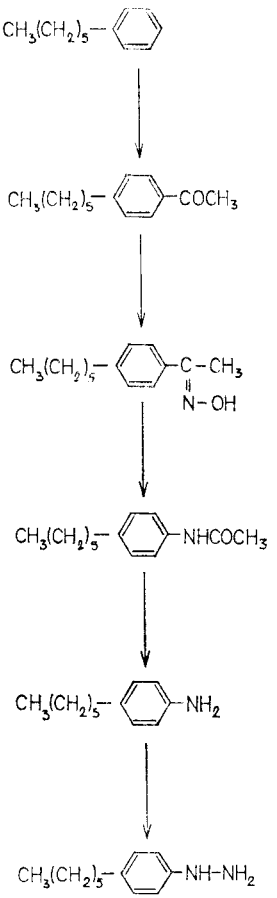
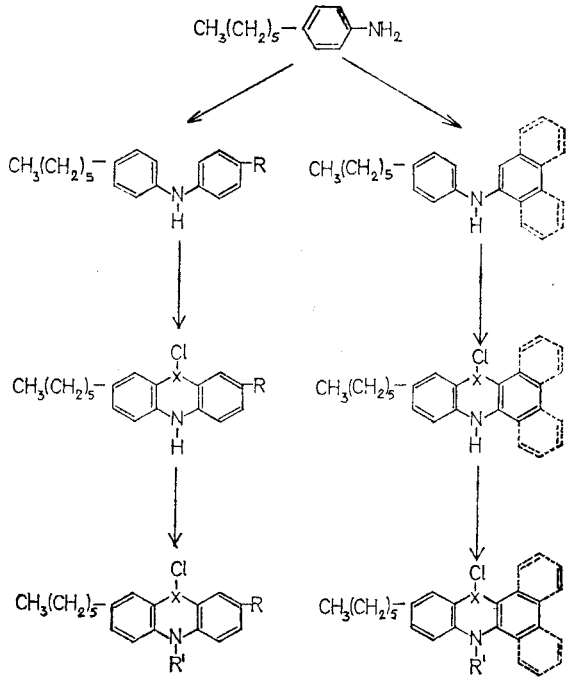


Fig. 1.

In order to obtain 4-(n-hexyl)aniline Beckmann[16] rearrangement of the corresponding oxime was carried out to 4-(n-hexyl)acetanilide, which, following hydrolysis, gave 4-(n-hexyl)aniline. The same was identified by its N-benzoyl derivative. 4-(n-hexyl)phenylhydrazine was obtained by diazotization (Fig. 1).

Investigations are now proceeding in several directions: 4-(n-hexyl)aniline with para substituted phenols and α- or β-naphthols by the method of Knoevenagel[13] gave the corresponding aromatic secondary amines. Using the modified method of Buu-Hoï and Lecocq[14], secondary amines with anhydride of CH_3COOH, or propionic acid in the presence of $ZnCl_2$, moderately heated for 24 hours, cyclized in the appropriate substituted acridines and benzoacridines which are identified by their picrates (Fig. 2).



x= S, As, Sb

R=-CH_3,-OCH_3,-Cl,-Br,-J

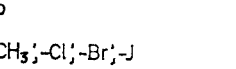
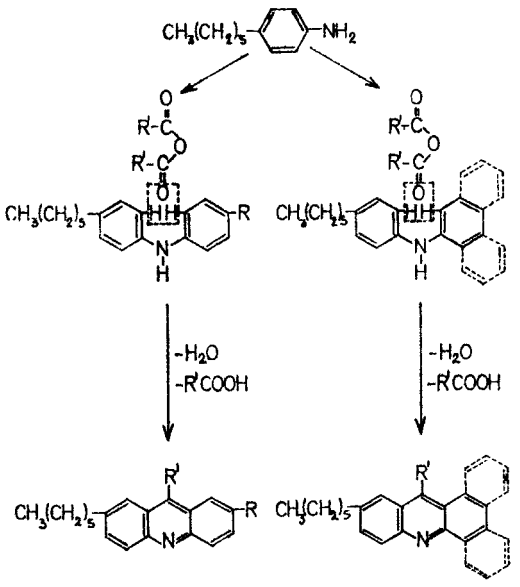
R'= CH_3CO-, 

Fig. 2.

Using the method of Wieland and Rheinheimer[17], secondary aromatic amines in reaction with $AsCl_3$ or $SbCl_3$, in the solution of orto-dichlorbenzene, were cyclized in the appropriate phenarsazines and phenstiboazines[18—21].

Aromatic secondary amines, also in reaction with sulfur and heated at predetermined temperature, cyclized in the appropriate phenothiazine derivative[22, 23]. Acylation was performed on these compounds of their NH-group, with acetyl or α- furoyl and 5-bromo-2-furoyl, and the appropriate acyl derivatives were obtained (Fig. 3).

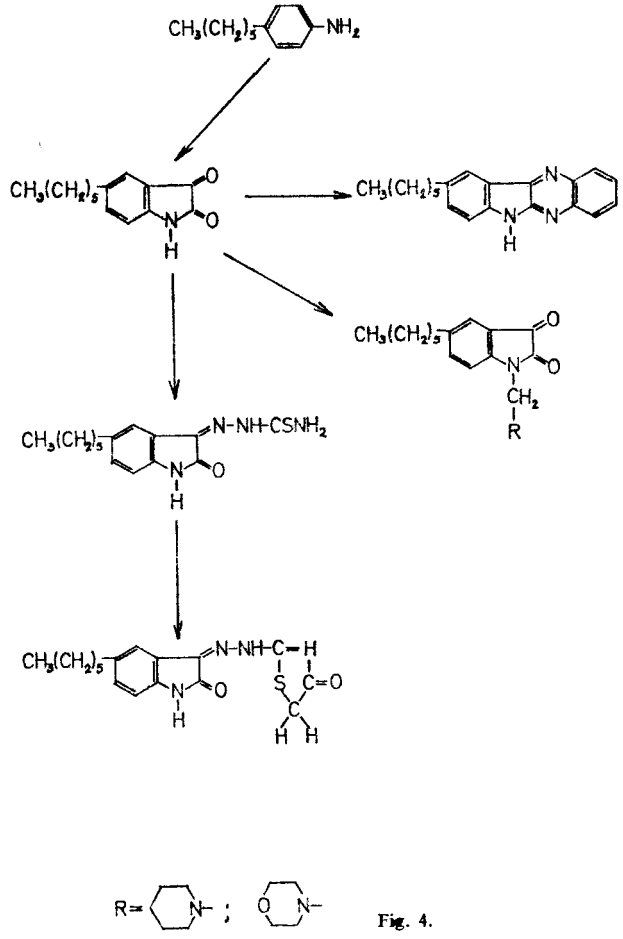
Using the Sandmeyer method[24], from 4-(n-hexyl)aniline with $NH_2OH.HCl$ and CCl_3-$CH(OH)_2$, the appropriate 5-(n-hexyl)isatin was obtained, which was



R=-CH_3; -OCH_3; -Cl; -Br; -J

R'=-CH_3; CH_3CH_2-

Fig. 3.

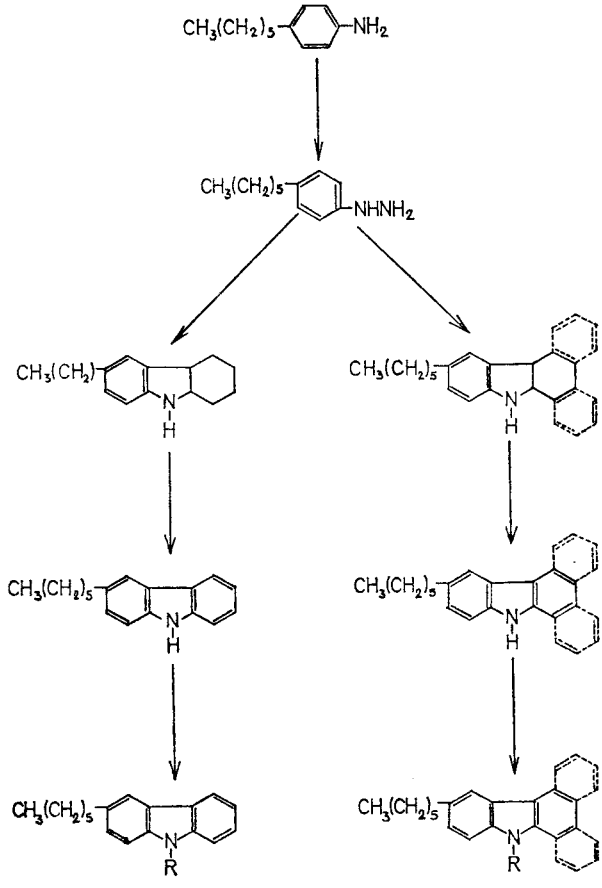


R=

Fig. 4.

identified by its thio-semicarbazone. In reaction with $CH_2ClCOOH$ in the propionic acid medium and in the presence of CH_3COONa, it was converted into the appropriate hydrazothiazolinone[25]. Also, with the reflux of equimolar quantity of 5-(n-hexyl)isatine and o-phenylenediamine in the acetic acid medium, the appropriate indophenazine was obtained[26].

At the same time, an equimolar quantity of 5-(n-hexyl)isatine, formaldehyde and piperidine or morpholine of the appropriate Mannich base was obtained ((Fig. 4).



R=CH_3CO-;  -CO-; Br-  -CO-

Fig. 5.

The investigations were extended with the aim of synthesizing the corresponding carbazole derivatives from 4-(n-hexyl)aniline. 4-(n-hexyl)aniline was converted through diazotization into 4-(n-hexyl)phenylhydrazine. which, with cyclohexanone, or α- and β-tetralone, gave the appropriate substituted hydrazones. With acetic acid (saturated with HCl) these were cyclized into appropriate tetrahydrocarbazoles. From them, with dehydrogenation in the presence

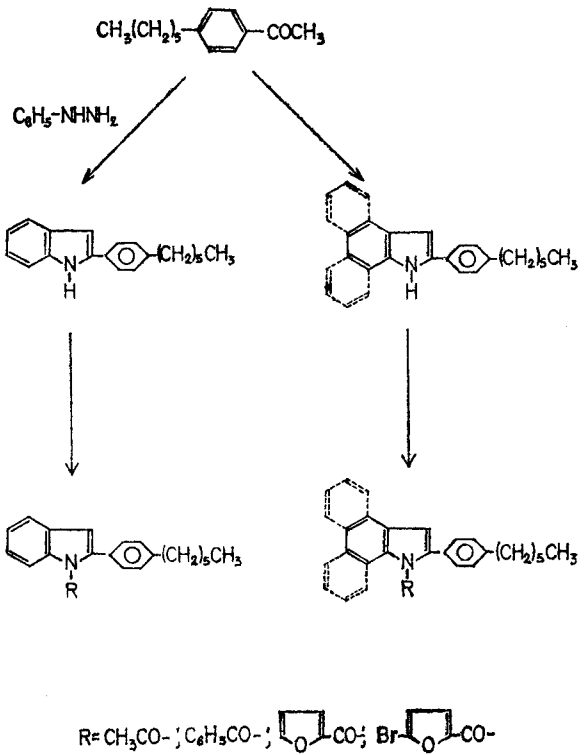

CH3(CH2)5
COCH3
C6H5-NHNH2
(CH2)5CH3
N
H
R
R= CH3CO-; C6H5CO-; CO-; Br- CO-

Fig. 6.

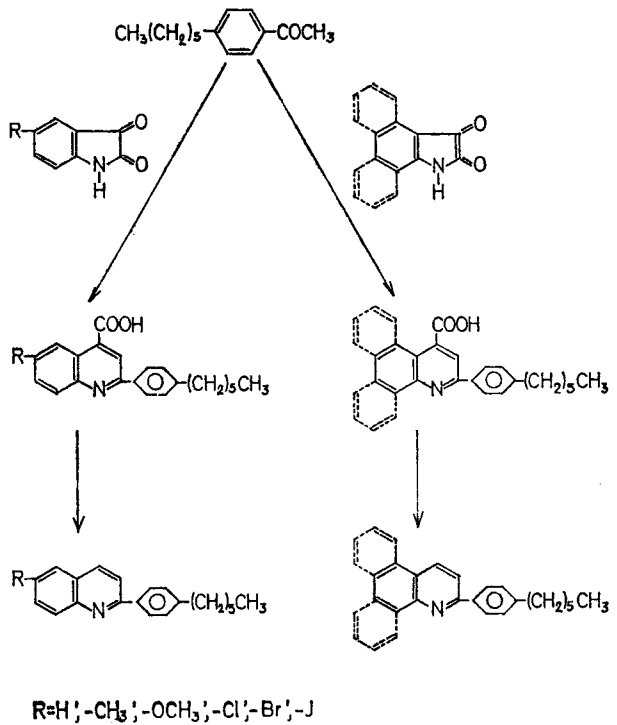

CH3(CH2)5
COCH3
R
O
N
H
COOH
(CH2)5CH3
R=H; -CH3; -OCH3; -Cl; -Br; -J

Fig. 7.

of 5% Pd on carbon were obtained apropriate carbazole derivatives which were identified by their picrates[27, 28]. Acylation with acetyl, or α-furoyl and 5-bromo-α-furoyl chloride, was performed and appropriate N-acyl derivatives were obtained (Fig. 5).

Using Fischer's method[27] 4-(n-hexyl)acetophenone with phenylhydrazine was converted into the appropriate hydrazone, and on heating in polyphosphoric acid 2-(4-n-hexylphenyl)indole was obtained. Analogous reaction was performed with α- and β-naphthyl hydrazine, and with the same procedure the appropriate benzoindoles were obtained (Fig. 6).

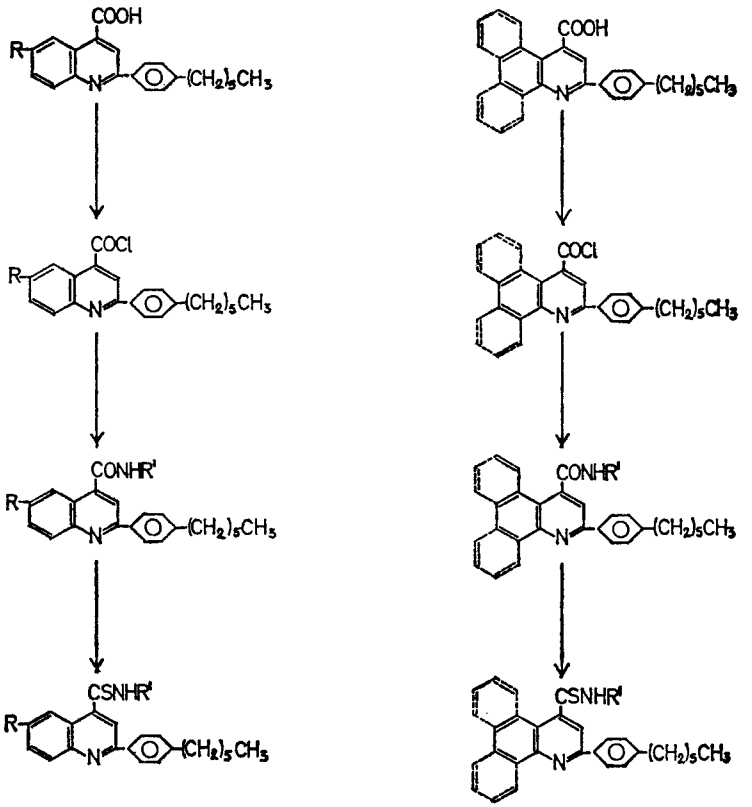


Fig. 8.

Using the Pfitzinger method[29], 4-(n-hexyl)acetophenone in reaction with isatin, or 5-substituted isatins and 4,5- and 6,7-benzoisatin in a solution of C_2H_5OH and KOH, heated for 24 hours, were cyclized in the appropriate substituted 2-(n-hexylphenyl)quinoline carboxylic acids. Their vacuum distilation in the presence of copper chrom oxide converted them into the appropriate 2-(n-hexylphenyl)-quinoline derivatives which were identified by their picrates (Fig. 7).

Next, the conversion of the carboxylic group with $SOCl_2$ or PCl_5 was performed and the appropriate chlorides of 2-(n-hexylphenyl)-quinoline-4-carboxylic acids were obtained, which were then promptly used in reaction with para substituted anilines in dry pyridine and were converted into the appropriate anilides of (2-(n-hexylphenyl)-quinoline-4-carboxylic acids. They were subsequently sulfonated with P_4S_{10} in dry pyridine, or dioxane by the method of Klingsberg and Papa[30] and were converted into N-substituted thioanilides of 2-(n-hexylphenyl)-4-quoinoline-4-carboxylic acids (Fig 8).

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ИЗВОД

Синтези во редот на некои кондензирани хетероциклични соединенија

М. Јанчевска-Николовска

Во продолжение врз испитувањата во областа на хетероцикличните соединенија од интерес беше да се синтетизираат кондензирани хетероциклични соединенија со н-хексил група како супституент.

За таа цел, изведени се реакции со н-хексил бензол со различни реактанти во различни реакциони услови и при тоа се синтетизирани преку интермедиери соответни кондензирани хетероциклични соединенија.

Реакционата способност на карактеристичните функционални групи во овие соединенија беше испитувана преку различни реакции.

Синтетизираните кондензирани хетероциклични соединенија и нивните деривати беа идентифицирани со елементарна микроанализа и инфрацрвените спектри.

ХЕМИСКИ ФАКУЛТЕТ
УНИВЕРЗИТЕТ »КИРИЛ И МЕТОДИЈ«
91000 СКОПЈЕ

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