STUDIES ON THE CHEMISTRY OF HETEROCYCLES

XLIX. CYCLIC MECHANISM OF THE ALKYLATION OF METAL DERIVATIVES OF BENZOLACTAMS

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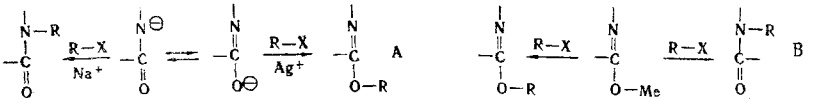
The mechanism of the aminoalkylation of sodium derivatives of γ-, δ-, and ε-benzolactams is discussed from the point of view of ideas on the formation of cyclic transition complexes.

The mechanism of the alkylation of ambident anions has already been the subject of lively discussions for several years. Particular attention has been devoted to metal derivatives of compounds with keto-enol tautomerism and considerably less to metal derivatives of lactams. Our ideas on the alkylation of the latter are based mainly on Baeyer's well-known investigations [1,2]. So far as concerns the mechanism of this reaction, both an ionic mechanism (A) [3] and a dual reaction mechanism (B) [4] have been discussed in the literature:



Kornblum [5] assumes that the silver salts of lactams, unlike the alkali–metal salts, contain a O^-Ag^+ ionogenic bond, the cation of which polarizes the C–X bond, as a result of which O-alkylation is ensured.

Mechanism A was tested by Nesmeyanov et al. [6-8], who showed that metal derivatives of carbonyl compounds have an enolic structure, the metal being bound to the oxygen by covalent bond, and they do not exhibit tautomerism. As applied to isatin, these conclusions were confirmed by Shigorin [9]. Mechanism B enjoys the greatest acceptance. In the case of silver salts of isatin, the possibility of the occurrence of the reaction through the state of the formation of a four-membered transition complex is suggested [4].

Recently, cyclic mechanisms have been attracting the attention of many workers and they have proved extremely fruitful for a number of reactions (the Claisen allyl rearrangement [10], the Kolbe reaction [11], and others). Conceptions of cyclic transition complexes have been used successfully by Syrkin [12] to interpret the mechanisms of the Kishner [Wolff–Kishner], Friedel–Crafts, Wurtz, Grignard, Knoevenagel, and other reactions. Reutov et al. [13], studying the influence of the nature of solvents on the ratio of products O- and C-alkylation, have shown the possibility of the occurrence of the reaction through the stage of the formation of both six- and four-membered cyclic complexes.

In the present work an attempt has been made to consider the mechanism of the alkylation of metal derivatives of the benzolactams I from the point of view of the formation of cyclic transition complexes.

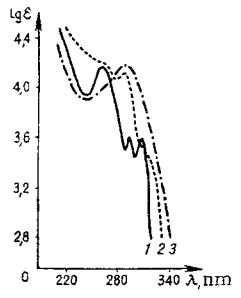


Fig. 1. UV spectra of II: 1) in C_2H_5OH; 2) in a 1 M solution of C_2H_5ONa in ethanol; 3) in conc. H_2SO_4.

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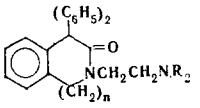
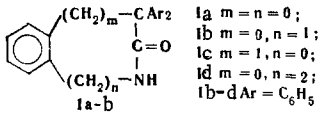
TABLE 1. N-Dialkylaminoethylbenzolactams

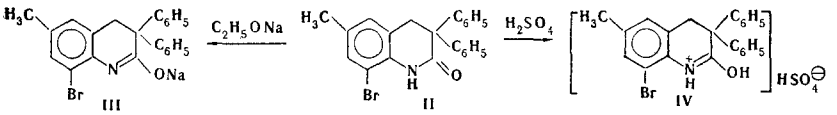


Compound	R	n	mp, °C* base	mp, °C* hydrochloride	mp, °C* methiodide	Empirical formula	N, % found	N, % calc.	Yield, %
XII	CH_3	1	114—115	268—270	240 (dec.)	$C_{25}H_{26}N_2O$	7,71	7,56	74,9
XIII	C_2H_5	1	—	209—211	217 "	$C_{27}H_{30}N_2O \cdot HCl$	7,18	7,03	51,5
XIV	CH_3	2	91—93	84—86†	213—215	$C_{26}H_{28}N_2O$	7,12	7,28	53

*All compounds were crystallized from ethanol.
† Sulfate.

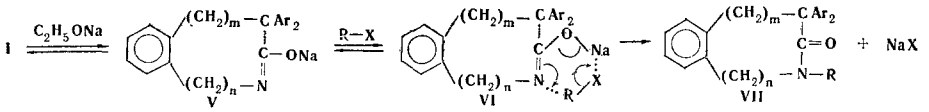


It has been shown [14] that Ia has the lactam structure in the free state, while its metal derivatives have the lactim structure. Similar results have been obtained for the benzolactam derivative Ic. The UV spectra of 8-bromo-6-methyl-3,3-diphenyl tetrahydroquinolin-2-one (II) (Fig. 1) in sodium ethoxide and concentrated sulfuric acid are displaced in the long-wave direction and have similar shapes, which shows a similarity of their structures and is explained by the formation of the lactim III and the salt IV, respectively.



The sodium derivatives of compounds I dissolve in hydrocarbons, which shows the presence of a covalent, and not an ionogenic, bond between the metal and the oxygen.

As the alkylating agents we selected $R_2N(CH_2)_2Cl$ ($R = CH_3$, C_2H_5). The alkylation of Ia takes place equally readily in the presence of sodium ethoxide and of solid caustic soda [15], while Ib and d are alkylated only in the presence of sodium ethoxide. This is explained by the higher acidity of Ia and of Ib and d (see [16]). The alkylation of sodium derivatives of I forms products of N-alkylation (Table 1). They are colorless crystalline substances of basic nature; their salts and methiodides are readily soluble in water. The mechanism of the alkylation of I with the assumption of a quasi-6-membered cyclic complex can be represented by the following scheme:



The reaction of the lactim V with R—X forms a transition complex VI in which the electronic transitions take place synchronously over the whole of the 6-membered ring. According to Syrkin [17], transition complexes have a planar or almost planar structure and mechanisms involving their formation are particularly favored energetically.

We assumed that valuable information to confirm the mechanism described above can be obtained by performing experiments with spatially complicated compounds I. With this object, we used compounds VIII-XI (see scheme, top of page 619).

7-Methyl-3,3-diphenyl-1,2,3,6,7-pentahydrobenzazepin-2-one (XI) was obtained by acidochromic condensation of N-(α-methyl-β-phenylethyl)benzilamide.

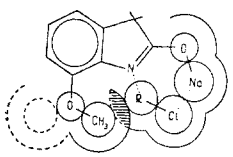


Fig. 2

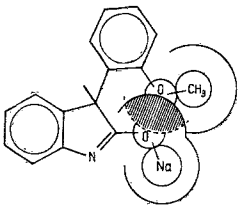


Fig. 3

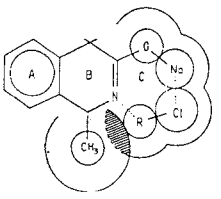
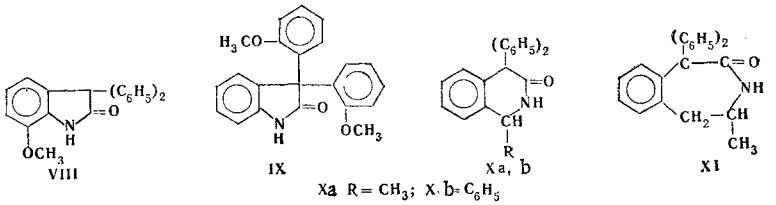


Fig. 4

Fig. 2. Sketch of the structure of the transition complex of the sodium derivative of VIII and R−Cl.

Fig. 3. Sketch of the structure of a fragment of the molecule of the sodium derivative of IX.

Fig. 4. Sketch of the structure of a fragment of the transition complex of the sodium derivative of Xa and R−Cl. Rings A and C are planar [17]; ring B contains two double bonds and probably has a planar or almost-planar configuration.



VIII IX Xa, b

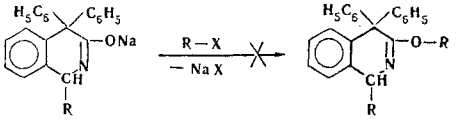
Xa $R = CH_3$; X. b $= C_6H_5$

XI

In VIII and IX, steric hindrance can be created by the substituents (CH_3O) of the benzene nuclei, and in X and XI by the substituents (R, CH_3) of the lactam rings. As our experiments have shown, the alkylation of I takes place successfully only when the formation of the complex VI is not hindered. When steric hindrance exists, however, alkylation is adversely affected or does not take place at all. Thus, in the alkylation of VIII and IX, the time of the experiments is increased from 4-5 h to 14 and 30 h, respectively [15].

It can be seen from Fig. 2 that when the CH_3 group is in the cis position with respect to the nitrogen the formation of VI is hindered, and only in the trans position (CH_3 denoted by dotted line) is steric hindrance absent. Figure 3 shows that when one of the two O-anisyl radicals rotates, the CH_3O group is superimposed on the O−Na group and hindrance to the formation of VI arises. The hindrance increases when substituents are introduced into the lactam rings of X and XI. In this case, the hindrance cannot be overcome and alkylation does not take place (Fig. 4).

Consequently, the alkylation of I takes place successfully only when the nitrogen and the metal are sterically accessible for the attacking molecule, i.e., when VI is formed. For example, the sodium derivatives X and XI do not form VI because the nitrogen of the lactim is highly screened by the neighboring substituent while at the same time the O−Na group is sterically accessible and the formation of O-alkylation products might be expected by the following scheme:



However, this reaction takes place in none of the experiments, which shows that the electronic transitions in the complex VI takes place considerably more readily than outside the complex.

The ideas that we have developed on the cyclic mechanism of the alkylation of metal derivatives of the benzolactams are in harmony with their structure as lactims and makes it possible to explain the steric hindrance shown in this reaction. The transfer of the reaction center takes place in the transition complex in agreement with Nesmeyanov and Kabachnik's results [4].

EXPERIMENTAL

2-(β-Dimethylaminoethyl)-4,4-diphenyltetrahydroisoquinolin-3-one (XII). To the sodium ethoxide obtained from 0.23 g (0.01 g-atom) of sodium in 6 ml of absolute ethanol was added 3.0 g (0.01 mole) of Ib and 10 ml of dry toluene. The excess of ethanol was distilled off, and a solution of 1.07 g (0.01 mole) of dimethylaminoethyl chloride in 4 ml of toluene was added. The mixture was heated for 5 h and filtered, and the clear toluene solution was acidified with gaseous hydrogen chloride. The hydrochloride that deposited was filtered off and crystallized from ethanol. The base was obtained by treating an aqueous solution of the hydrochloride with ammonia.

N-(α-Methyl-β-phenylethyl)benzilamide (XV). To the phenylmagnesium bromide obtained from 23.55 g (0.15 mole) of bromobenzene and 3.65 g (0.15 g-atom) of magnesium in 75 ml of ether was added 12.5 g (0.05 mole) of ethyl α-methyl-β-phenylethyloxamate in 50 ml of ether, and the mixture was heated in a water bath for 30 min. The organomagnesium complex was decomposed with dilute hydrochloric acid. The ethereal layer was separated off and treated with steam. Yield 12.43 g (63.7%). Plates (from ethanol) with mp 114-115°C. Found %: N 4.42. $C_{23}H_{23}NO_2$. Calculated %: N 4.04.

7-Methyl-3,3-diphenyl-1,2,3,6,7-pentahydrobenzazepin-2-one (XI). A solution of 6.9 g (0.02 mole) of XV in 40 ml of glacial acetic acid was treated with 50 ml of conc. H_2SO_4. A rapidly disappearing coloration arose. The mixture was poured into 200 ml of water, and the precipitate was filtered off and crystallized. Yield 4.93 g (75.4%). Plates (from ethanol) with mp 203-204°C. Found %: N 4.41. $C_{23}H_{21}NO$. Calculated %: N 4.28.

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