INVESTIGATIONS IN HETEROCYCLIC CHEMISTRY

XLIV. Comparative Ease of Ring-Closure of Five- and Six-Membered Heterocycles in the Acid Condensation of Arylides of Diarylglycolic Acids*

P. A. Petyunin, A. K. Sukhomlinov, and N. G. Panferova

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 6, pp. 1033–1037, 1968

UDC 547.7+66.062.652.2+535

With the acid condensation of diarylglycolic benzylanilides as an example, it has been shown that the predominant formation of a five-membered ring rather than a six-membered ring takes place even in the case where the internal structure of the anilide permits the simultaneous formation of both rings. It has also been shown that it is possible to determine the size of the ring formed on condensation from the UV and IR spectra, and the presence of hydrogen bonds in the arylamides of diarylglycolic acids and the formation of the lactim form and of the quatenary ammonium salt of the base of 3, 3-diphenyloxindole in solutions of sodium ethoxide and concentrated H_2SO_4, respectively, have been confirmed.

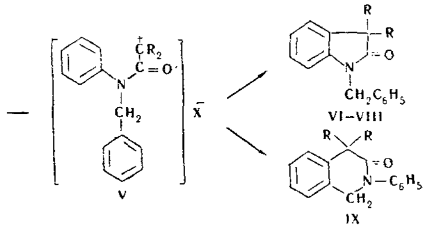
It has been shown previously [1–3] that in the acid condensation of arylides of hydroxy carboxylic acids the rate of ring closure falls in the sequence: 5 > 6 > > 7 > 8. It was interesting to determine to what extent this feature is observed in the case where the internal structure of the arylide permits the formation of rings of different sizes. For arylcarboxylic acids, for example, it is known that six-membered rings are formed more easily than five-membered rings [4].

The present investigation was devoted to a study of the comparative ease of closure of five- and six-membered rings in the arylides of diarylglycolic acids.

As subjects, we used the diarylglycolic N-benzylanilides II–IV, the synthesis of which was effected by the reaction of ethyl N-benzyloxanilate I with Grignard compounds (RMgX, R = C_6H_5, 4-$CH_3C_6H_4$, 2-$CH_3OC_6H_4$) (Table 1). They are crystalline substances soluble in the usual organic solvents; with concentrated H_2SO_4 they give a coloration which rapidly disappears (halochromism).

$C_6H_5CH_2N(C_6H_5)COCOOC_2H_5 \longrightarrow C_6H_5CH_2N(C_6H_5)COC(OH)R_2 \longrightarrow$

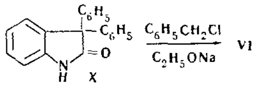
I II–IV



V VI–VIII IX

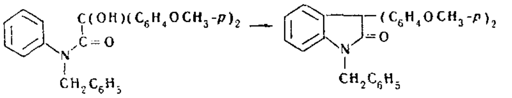
The arylides II–IV contain two nucleophilic radicals (N-phenyl and N-benzyl) and therefore, in the cation of the halochromic salt V, ring closure may lead both to a five-membered (oxindole) ring VI–VIII and to a six-membered (3-oxotetrahydroisoquinoline) ring IX. This possibility also depends on the nature of the radicals present on the carbinol carbon [5].

Experiments showed that, in the acid condensation of the arylides II–IV, 1-benzyl-3, 3-diaryloxindoles VI–VIII are formed (Table 2). The structure of the latter was shown by the independent synthesis of one of them (VI), which was obtained by the benzylation of 3, 3-diphenyloxindole X, and also by the UV and IR absorption spectra of VI (curve 3, Fig. 3; $\nu_{C=O}$ 1700 cm^{-1}). They are crystalline substances with higher melting points than the initial arylides



X VI

In addition, to prove the predominant formation of the five-membered ring rather than the six-membered ring, the acid condensation of N-benzyl-4, 4'-dimethoxybenzilanilide (XI) was carried out. This was condensed by means of formic acid without preliminary isolation [6]. According to the literature [3], in XI only the five-membered ring can form, giving 1-benzyl-3, 3-di(p-anisyl)oxindole (XII).



XI XII

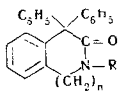
An attempt was made to use spectroscopic methods to determine the size of the rings formed. The UV and IR absorption spectra of the benzilic acid arylides (II, XIII–XVIII) and the products of their acid condensation (X, XIX–XXI) were studied.

$(C_6H_5)_2CR'CONR(CH_2)_nC_6H_5$

XIII R=H, R'=OH, n=0;

XV R=H, R'=OH, n=1;

XVII R=CH_3, R'=H, n=0;



XIV R=CH_3, R'=OH, n=0;

XVI R=H, R'=OH, n=2;

XVIII R=H, R'=CH_3O, n=0.

XIX R=CH_3, n=0;

XX R=H, n=1;

XXI R=H, n=2.

The tertiary arylamides XXII are feebly associated (in the crystalline state, XIV gives bands at 3560 and 1621 cm^{-1} of bound HO and CO groups) and, in spite of statements in the literature [7], do not contain intramolecular hydrogen bonds. This is confirmed by the similarity of the UV absorption spectra of II and

---

*For part XLIII, see [17].

Table 1

Melting Points, Yields, and Analytical Results for the Diarylglycolic N-Benzylanilides

Compound	Name	Mp, ° C*	Empirical formula	N, %		yield, %	Coloration with conc H_2SO_4
				found	calculated		
II	N-Benzylbenzilanilide	88—89	$C_{27}H_{23}NO_2$	3.62 3.70	3.56	85.2	Yellow
III	N-Benzyl-4,4'-dimethylbenzilanilide	126—127	$C_{29}H_{27}NO_2$	3.13 3.21	3.32	93.1	Crimson
IV	N-Benzyl-2,2'-dimethylbenzilanilide	112—113	$C_{29}H_{27}NO_4$	3.07 3.20	3.09	90.5	Green

---

*Compounds II and IV were crystallized from ethanol and III from glacial acetic acid.

Table 2

Melting Points, Yields, and Analytical Results for the Oxindole Derivatives

Compound	Name	Mp, ° C (from ethanol)	Empirical formula	N, %		Yield, %
				found	calculated	
VI	1-Benzyl-3,3-diphenyloxindole	163	$C_{27}H_{21}NO$	3.68 3.70	3.73	100
VII	1-Benzyl-3,3-di(p-tolyl)oxindole	154	$C_{29}H_{25}NO$	3.38 3.46	3.47	98.3
VIII	1-Benzyl-3,3-di-(o-anisyl)oxindole	191	$C_{29}H_{25}NO_3$	3.15 3.26	3.21	96.2

Table 3

IR Absorption Spectra of the Cyclic Lactams

Compound	Position of the absorption maxima in the region of the C=O stretching vibrations, cm^{-1}	Δν, cm^{-1}	Size of the ring
X	1716 } 1711	—	
XIX	1706 }	—	5
XX	1667	44	6
XXI	1645	66	7

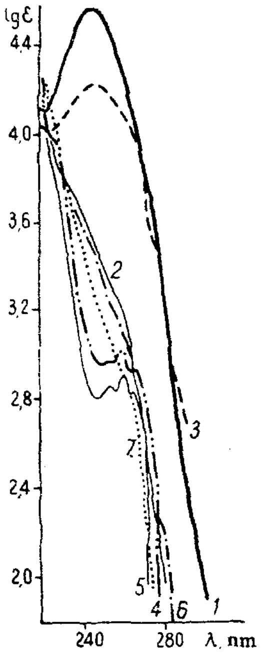


Fig. 1. UV absorption spectra in ethanol: 1) **XIII**; 2) **XIV**; 3) **XVIII**; 4) **XV**; 5) **XVI**; 6) **II**; 7) **XVII**.

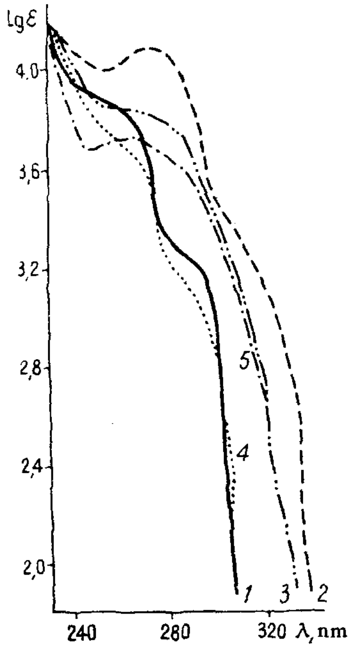


Fig. 2. UV absorption spectra: 1) **X** (in ethanol); 2) **X** (in 1 M C_2H_5ONa); 3) **X** (in conc H_2SO_4); 4) **XIX** (in 1 M C_2H_5ONa); 5) **XIX** (in conc H_2SO_4).

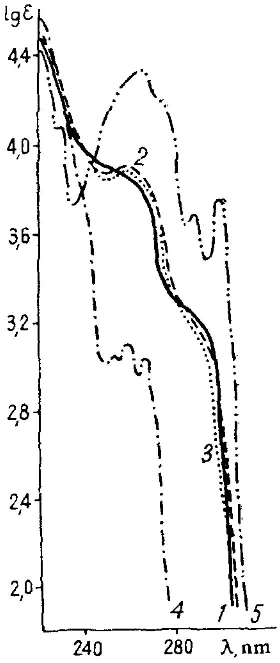
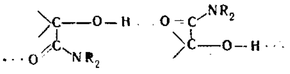


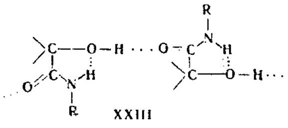
Fig. 3. UV absorption spectra in ethanol: 1) **X**; 2) **XIX**; 3) **VI**; 4) **XX**; 5) **XXI**.

XIV to that of XVII (in the latter, the formation of hydrogen bonds is excluded) (Fig. 1), and also by the presence in the IR spectrum of XIV in CCl_4 solution of bands at 3610 and 1640 cm^{-1} of nonbound HO and CO groups [8–10].

The secondary arylamides (XXIII) show the presence of weak intermolecular hydrogen bonds (in the crystalline state, XIII gives bands at 1665 and 3560 cm^{-1} of bound CO and HO groups) and of strong intramolecular hydrogen bonds (the UV spectra of XIII and XVIII are displaced in the long-wave direction [11–13], and the IR spectra have bands at 3610, 1700–1692, and 3405–3400 cm^{-1} of free HO and CO groups and bound NH groups, respectively), which agrees with data in the literature [14]. The absorption curves of XV and XVI are displaced in the shortwave direction, which is explained by a disturbance of the conjugation between the nitrogen atom and the benzene ring because of the introduction of the methylene groups.

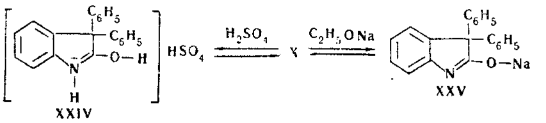


XXII



XXIII

The UV absorption spectra of X in concentrated H_2SO_4 and sodium ethoxide are displaced by 25–30 nm in the long-wave direction (Fig. 2), which is explained by salt formation in the first case XXIV and by a tautomeric transformation in the second case XXV.



The N-methyl derivative XIX undergoes no change in sodium ethoxide but in concentrated H_2SO_4 it absorbs similarly to X.

The UV spectra (Fig. 3) and the IR absorption spectra (Table 3) of 5-, 6-, and 7-membered cyclic lactams have such clear differences that they can easily be used to identify the size of the rings formed in the acid condensation of arylides of diarylglycolic acids.

EXPERIMENTAL

The UV spectra were taken on an SF-4A instrument at concentrations of $2 \cdot 10^{-3}$–$2 \cdot 10^{-5}$ M. The IR spectra were recorded on an IKS-14 instrument with LiF and NaCl prisms in tablets with KBr (concentration of the substance 0.5%) [15] and in CCl_4 solution (concentrations 0.002 M).

Ethyl N-benzyloxanilate (I). To a solution of 76.7 g (0.42 mole) of N-benzylaniline in 100 ml of ether was added 28.5 g (0.21 mole) of the ethyl ester–chloride of oxalic acid. The mixture was heated in the water bath for 30 min, 100 ml of water was added, and the ethereal layer was separated off and dried. After evaporation of the solvent, the residue was distilled at 196–198° C (5 mm); yield 41.3 g or 34.7%, calculated on the amine. Viscous oil, rapidly solidifying. Rods (from gasoline) with mp 55–56° C. Found, %: N 4.82, 4.76. Calculated for $C_{17}H_{17}NO_3$, %: N 4.94.

N-Benzylbenzilanilide (II). To the phenylmagnesium bromide obtained from 6.28 g (0.04 mole) of bromobenzene and 0.97 g (0.04 g-at.) of magnesium in 20 ml of ether was added 2.83 g (0.01 mole) of I in 20 ml of ether and the mixture was heated in the water bath for 1 hr. The organomagnesium complex was decomposed with a saturated solution of NH_4Cl. The ethereal layer was separated off and treated with steam. Yield 3.4 g.

1-Benzyl-3,3-diphenyloxindole (VI). a) A solution of 0.5 g (1.27 mole) of II in 5 ml of glacial CH_3COOH was treated with 5 ml of conc H_2SO_4. A yellowish coloration appeared which rapidly disappeared. The mixture was poured into 20 ml of water, and the precipitate was filtered off and crystallized. Yield 0.48 g.

b) To the sodium ethoxide obtained from 0.11 g (0.005 g-at) of sodium and 3 ml of ethanol were added 4 ml of xylene and 1.4 g (0.005 mole) of X. The excess of ethanol was distilled off, and 1 g (0.007 mole) of benzyl chloride in 2 ml of xylene was added. The mixture was heated for 5 hr and the precipitate was filtered off and dried in the air. Yield 1.45 g (78.8%). Needles (from C_2H_5OH) with mp 164° C. A mixture with the substance obtained in the previous experiment showed no depression of the melting point.

1-Benzyl-3,3-di(p-anisyl)oxindole (XII). The starting materials were 1.41 g (0.005 mole) of I, 2.8 g (0.015 mole) of p-bromoanisole, and 0.36 g (0.015 g-at) of magnesium in 20 ml of ether. The ethereal layer was treated with steam, the residue was dissolved in 15 ml of glacial CH_3COOH, and 85% formic acid was added until a red-violet color ceased to appear. Then the mixture was poured into 50 ml of water and the precipitate was treated as described above. Yield 1.65 g (76.4%). Needles (from ethanol) with mp 163–164° C. Found, %: N 3.34, 3.28. Calculated for $C_{29}H_{25}NO_3$, %: N 3.21.

N-Methylbenzilanilide (XIV) was obtained in 75.3% yield from monomethylaniline and chlorodiphenylacetyl chloride with the subsequent replacement of the chlorine in the N-methylchlorodiphenylacetanilide by hydroxyl. Needles (from gasoline) with mp 106–107° C.

N-Methyldiphenylacetanilide (XVII) was obtained by the reaction of diphenylacetyl chloride with monomethylaniline in pyridine. Plates (from ethanol) with mp 102° C. Found, %: N 4.83, 4.71. Calculated for $C_{21}H_{19}NO$, %: N 4.66.

1-Methyl-3, 3-diphenyloxindole (XIX). a) Obtained with a yield of 93% by the acid condensation of XIV. Plates (from ethanol) with mp 176–177° C [16].

b) To a solution of 4.28 g (0.04 mole) of N-methylaniline in 40 ml of ether was added an ethereal solution of 5.3 g (0.02 mole) of chlorodiphenylacetyl chloride. The solvent was driven off from the filtrate and the residue was dissolved in methanol with heating. After 24 hr, the precipitate that had deposited was filtered off and crystallized from ethanol. Yield 5.2 g (90%), mp 176–177° C. A mixture with an authentic sample gave no depression of the melting point.

REFERENCES

1. P. A. Petyunin and N. G. Panferova, ZhOKh, 17, 502, 1947.
2. P. A. Petyunin, ZhOKh, 22, 700, 1952.
3. P. A. Petyunin and V. S. Shklyaev, ZhOKh, 23, 853, 1953.
4. W. S. Johnson, Organic Reactions, Vol. 2, [Russian translation], IL, 129, 1950.
5. P. A. Petyunin and N. G. Panferova, KhGS [Chemistry of Heterocyclic Compounds], 2, 734, 1966.
6. P. A. Petyunin and A. F. Soldatova, KhGS [Chemistry of Heterocyclic Compounds], 1, 261, 1965.
7. V. S. Shklyaev, ZhOKh, 35, 1966, 1965.
8. A. Cross, An Introduction to Practical Infrared Spectroscopy [Russian translation], IL, 96, 1961.
9. K. Nakanishi, Absorption Spectroscopy. Practical [Russian translation], Mir, pp. 37, 58, 1965.
10. L. Bellamy, Infrared Spectra of Complex Molecules [Russian translation], IL, p. 293, 1963.

11. T. I. Temnikova, Course of the Theoretical Principles of Organic Chemistry [in Russian], Goskhimizdat, p. 168, 1959.
12. G. Pimentel and O. MacClellan, The Hydrogen Bond [Russian translation], Mir, p. 160, 1964.
13. A. E. Lutskii, Usp. khim., 23, 479, 1954.
14. S. L. Shapiro, I. M. Rose, and L. Freedmann, J. Am. Chem. Soc., 23, 6822, 1959.
15. A. A. Boldin and R. F. Vasil'ev, Zav. lab., 7, 12, 1961.
16. B. Witkop, and A. Ek, J. Am. Chem. Soc., 73, 5664, 1951.
17. M. E. Konshin and P. A. Petyunin, KhGS collection 1, 310, 1967.

11 July 1966

Khar'kov Pharmaceutical Institute

Perm Pharmaceutical Institute