UDC 547.838.1

STUDIES ON CERAMIDONE DERIVATIVES

II. 8-Hydroxy and 8-Arylaminoceramid-9-one

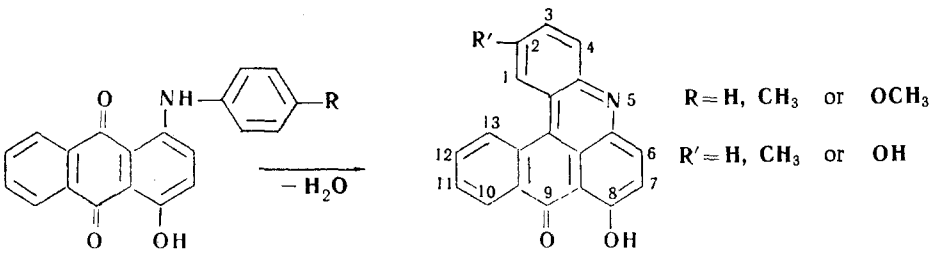
N. I. Grineva, V. V. Puchkova, and V. N. Ufimtsev

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 2, No. 5, pp. 744–748, 1966

The synthesis, arylamination and other reactions of ceramid-9-one are described. 8-Hydroxyceramid-9-one is converted to the corresponding 8-arylaminoceramid-9-one by heating with excess aromatic amine in the presence of boric acid. The latter compound, on heating with either polyphosphoric or sulfuric acid, is hydrolyzed to the original 8-hydroxyceramid-9-one.

We have previously studied the dehydration of 1,4-diarylamino- and 1-hydroxy-4-p-tolylaminoanthraquinones to the corresponding ceramid-9-ones [1], which might be useful as intermediates in the synthesis of dyes for synthetic fibers. The present work reports the synthesis, arylamination, and other reactions of ceramid-9-one derivatives (in the Ring Index nomenclature 9H-naphth [3, 2, 1-k, 1] acridone-9).

The starting material, 8-hyroxyceramid-9-one, was obtained by heating 1-hydroxy-4-arylaminoanthraquinone from 130° to 170° with 70% sulfuric acid.



Under these conditions, cyclization of 1-hydroxy-4-p-tolylaminoanthraquinone takes place quantitatively, in 12 hours, with the formation of 8-hydroxy-2-methylceramid-9-one (I). Cyclization of 1,4-diarylaminoanthraquinone to 8-arylaminoceramid-9-one is 8 to 10 times faster, while in the absence of substitution on position 4, 1-arylaminoanthraquinone cyclizes to ceramid-9-one somewhat more slowly than 1,4-diarylaminoanthraquinone. The ease of cyclization to the ceramidone heterocycle is therefore dependent on the substituent on position 4 of the anthraquinone molecule in the order: arylamino > H > OH.

The cyclization of 1-hydroxy-4-p-methoxyphenylaminoanthraquinone takes considerably longer, with simultaneous hydrolysis of the methoxyl group, giving 2, 8-dihydroxyceramid-9-one (II). An analogous hydrolysis of methoxyl groups was observed [2] during the cyclization of 1-methoxyphenylamino- and 1,5-dimethoxyphenylaminoanthraquinone.

The cyclization of 1-hydroxy-4-phenylaminoanthraquinone is accompanied by sulfonation: 46.5 % 8-hydroxyceramid-9-one sulfonic acid and only 31% unsulfonated 8-hyroxyceramid-9-one (III) are isolated from the reaction mixture. Apparently, as with many similar cases involving the anthraquinone nucleus, sulfonation occurs on the benzene nucleus of the quinoline heterocycle. In the cyclization of 1-phenylaminoanthraquinone, the main product of the reaction is the sulfonic acid; the unsulfonated ceramid-9-one being obtained in only 15.4% yield. Similarly, in the cyclization of 1,4-diphenylaminoanthraquinone, the sulfonic acid is also obtained.

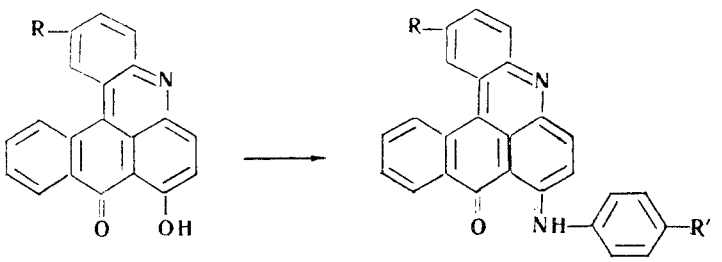
8-Hydroxyceramid-9-one is insoluble in aqueous alkali, although its color changes from yellow to red. Solution in alcoholic alkali gives an orange-red coloration, the initial hydroxyceramidone being precipitated on acidification. II is soluble in aqueous solutions of sodium hydroxide, ammonia and sodium carbonate at a pH of 9 or above, and is reprecipitated unchanged upon dilution with water or acidification.

On heating 8-hydroxyceramid-9-one with excess aromatic amines in the presence of boric acid at 145° to 230° C, the hydroxyl group in position 8 is replaced by an arylamino group. The 8-arylaminoceramid-9-one series is obtained in this way (see table). This arylamination takes place readily with p-anisidine

Arylamination of 8-Hydroxyceramid-9-one and Properties of the 8-Arylaminoceramido-9-ones

Starting materials		Reaction conditions		Products	Mp, °C (solvent)	Appearance	Empirical formula	Found, %				Calculated, %				Yield %
Ceramidones	Arylamines	Temp., °C	Time, min					C	H	N	Cl	C	H	N	Cl	
I	p-Toluidine	160	90	8-(4'-Tolylamino)-2-methylceramid-9-one	240.5—241.5 (benzene)*	Red platelets	$C_{28}H_{20}N_2O$	—		—						63.7
I	p-Chloroaniline	160	90	8-(4'-Chlorophenylamino-2-methylceramid-9-one	263.0—264.0 (butanol)	Orange platelets	$C_{27}H_{17}ClN_2O$	77.38 77.38	4.27 4.14	6.43 6.19	8.86 8.60	77.05 —	4.07 —	6.66 —	8.42 —	41.4
I	p-Nitroaniline	200—230	270	8-(4'-Nitrophenylamino)-2-methylceramid-9-one	304.8—305.4 (chlorobenzene)	Orange needles	$C_{27}H_{17}N_3O_3$	—	—	9.14 9.04	—	—	—	9.75	—	88.8
III	Aniline	160	90	8-Phenylaminoceramid-9-one	221.5—222.0 (benzene)*	Red prisms	$C_{26}H_{16}N_2O$	—	—	—	—	—	—	—	—	16.7
III	p-Anisidine	145	20	8-(4'-Methoxyphenylamino)-ceramid-9-one	196.5—197.0 (CCl_4 and sublimation)	Red crystals	$C_{27}H_{18}N_2O_2$	80.62	4.35	6.56 6.50	—	80.58	4.51	6.96	—	67.2

* Identification by mixed melting point with products obtained from cyclization of the corresponding 1, 4-diarylaminoanthraquinones.



R=H or CH_3; R′=H, CH_3, OCH_3, Cl or NO_2.

(yield 67% at 145°), p-toluidine (63% at 160°), and p-chloroaniline (41.5% at 160°). With p-nitroaniline, however, arylamination proceeds with difficulty only at temperatures above 200° C.

The arylamination of 8-hydroxyceramid-9-one allows one to obtain 8-arylaminoceramid-9-one with different substituents on the arylamino group than the original compounds, which were substituted on positions 1, 2, 3, and 4. This method is of especial interest for the synthesis of substituted 8-arylaminoceramid-9-one derivatives, which are stable to acids at high temperatures.

During prolonged heating in concentrated or dilute acids, the 8-arylaminoceramid-9-ones are hydrolyzed to 8-hydroxyceramid-9-one. Previously, in an attempt to obtain cerodiamidine from double cyclization of 1, 4-di-p-tolylaminoanthraquinone by heating to 160° C in polyphosphoric acid, it was found that increase of the reaction time from one to four hours did not give the expected product. Instead, the yield of the intermediate 8-p-tolylamino-2-methylceramid-9-one (IV) dropped from 95 to 32%, and I could now also be isolated from the reaction products. Heating IV to 160° in polyphosphoric acid for 12 hours hydrolyzed it to I in 63% yield, while refluxing (13 hours at 170°) with 61% sulfuric acid gave 26% hydrolysis.

Experimental

Ceramid-9-one (V). 2 g (6.7 mmole) 1-phenylaminoanthraquinone in 60 ml of 70% sulfuric acid was heated for 3.5 hours at 130°, poured into ice-water, the ceramid-9-one sulfonic acid was filtered off, the filtrate neutralized with a solution of sodium hydroxide, and the precipitate filtered, washed and dried. The yield of V was 0.29 g (15.4%), yellow platelets, mp 204°–206° C (from dilute methanol) (lit. mp 206° [3]).

Similarly, 2-methylceramid-9-one, yellow platelets, mp 165°–166.5° C (from alcohol) was obtained from 1-p-tolylaminoanthraquinone by heating five hours at 130°. Found: C 84.94, 85.18; H 4.49, 4.20; N 4.75, 4.50%. Calculated for $C_{21}H_{13}NO$: C 85.41; H 4.45; N 4.76%.

8-Hydroxyceramid-9-one (III). 14.28 g (45 mmole) 1-hydroxy-4-phenylanthraquinone and 200 ml 70% sulfuric acid was heated for 12 hours at 130°, and poured into 700 ml of ice-water, the precipitate was filtered off, washed with a little cold water, stirred with 10% sodium hydroxide, diluted with water, again filtered, and washed on the filter with 2% NaOH, and then water, until neutral. The dried precipitate was extracted with benzene, from which 3.08 g of III was obtained by evaporation. The residue was extracted with hot acetic acid, giving 0.78 g of III, for a total yield of 3.86 g (31.2%), yellow needles, mp 207.5°–208° C (from CCl_4). It was readily soluble in acetic acid, chloroform and benzene, and with difficulty, in alcohol. It was soluble in conc H_2SO_4, with the formation of a reddish color. Found: C 80.99, 80.90; H 3.54, 3.29; N 5.31, 5.20%. Calculated for $C_{20}H_{11}NO_2$: C 80.80; H 3.73; N 4.71%.

From the alkaline filtrate, on acidification with conc HCl, was obtained 7.23 g (46.5%) of 8-hydroxyceramid-9-one sulfonic acid, orange crystals, sol. in water, alkali and bicarbonate solutions, precipitating on reacidification or salting out with sodium chloride.

2,8-Dihydroxyceramid-9-one (II). 15 g (43 mmole) 1-hydroxy-4-methoxyphenylaminoanthraquinone in 200 ml of 70% sulfuric acid was heated 31 hours at 130°, poured into ice-water, the precipitate filtered off, and washed with water until neutral, to give 12.61 g (92.8%) of II, orange needles, mp 336°–337° C (from nitrobenzene). It was soluble in aqueous NaOH, ammonia and carbonate solutions at a pH of 9 or higher, insoluble in most common organic solvents, but readily soluble in pyridine and dimethylformamide, less so in chlorobenzene and nitrobenzene. It was also soluble in conc. sulfuric acid, giving an olive coloration. A sample for analysis was vacuum-sublimed. Found: C 75.56, 75.86; H 3.43, 3.44; N 4.63, 4.77%. Calculated for $C_{20}H_{11}NO_3$: C 76.67; H 3.54; N 4.48%.

3.8 g (12 mmole) II was refluxed with 400 ml glacial acetic acid, cooled, and filtered go give 4.27 g (94.7%) of the acetate salt of II, dark orange platelets, mp 320°–321° C (from glacial acetic acid). This was soluble in cold water and sodium hydroxide solutions, neutralization of these solutions gave a quantitative recovery of II. Found: C 71.01, 70.76; H 3.87, 4.00; N 3.42, 3.65%. Calculated for $C_{20}H_{11}NO_3 \cdot C_2H_4O_2$: C 70.77; H 4.05; N 3.75%.

8-(4'-Methoxyphenylamino)-2-methylceramid-9-one (VI). 1.5 g (4.8 mmole) I, 21 g (0.18 mmole) p-anisidine, and 1.5 g (25 mmole) boric acid were heated for 1.5 hours at 145°–147°, then cooled to 100°. The reaction mass was treated with 10% HCl, the precipitate filtered off, then stirred successively with 10% HCl, water, 10% NaOH, and water, and dried. The solid was dissolved in chloroform and chromatographed on aluminum oxide, using chloroform as developer. The dark red lower zone on the column was extracted with hot chloroform and evaporation of the solution gave 1.33 g (66.2%) of VI, red needles, mp 203°–203.5° C (from butanol). It was readily soluble in acetone, dimethylformamide and hot chloroform, less so in alcohol and benzene. Found: C 80.10, 80.30; H 5.12, 5.14; N 6.65, 6.95%. Calculated for $C_{28}H_{20}N_2O_2$: C 80.75; H 4.84; N 6.73%.

In a similar manner I was arylaminated with p-toluidine, p-chloroaniline, and p-nitroaniline, and III with aniline and p-anisidine. The results of these experiments are given in the table.

Hydrolysis of 8-p-tolylamino-2-methylceramid-9-one (IV). 0.40 g (1 mmole) of IV and 40 ml of 61% sulfuric acid was heated 13 hours at 170°–172°, the original violet color changing to yellow-brown. After cooling, the solid was filtered off and stirred with 61% sulfuric acid and water; alkali was then added to bring the pH to 8. The solid was filtered, washed with water, and dried, giving 0.295 g of the starting material IV, mp 236°–237° C. The filtrate and wash liquids were diluted with water, 50% KOH was added until a neutral reaction to Congo red was obtained, and the yellow precipitate filtered off, washed and dried, giving 0.81 g of I, mp 189°–190° (from CCl_4). The yield was quantitative based on the recovered IV.

REFERENCES

1. N. I. Grineva, V. V. Puchkova, and V. N. Ufimtsev, ZhOKh, **33**, 597, 1963.
2. A. H. Cook and W. Waddington, J. Chem. Soc., 402, 1945.
3. H. Decker, Ann., **348**, 242, 1906.

2 March 1965

Scientific Research Institute of Organic Intermediates and Dyes, Moscow