MACROCYCLIC AMIDOACYLHYDRAZONES

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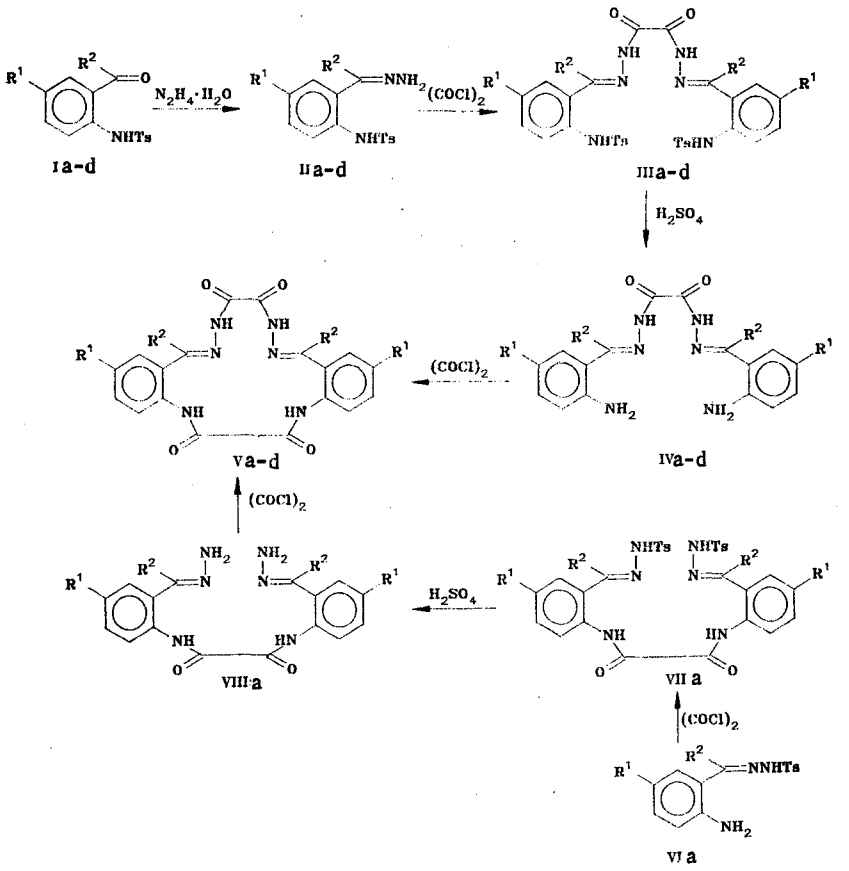
Substituted dibenzo[d,j][1,2,6,9,13,14]hexaazahexadeca-2,4,10,12-tetraene-7,8-15,16-tetraones have been obtained from hydrazones of ortho-acyltosylanilines. The structure of the former has been demonstrated by IR, PMR, and mass spectra and by alternative synthesis.

In recent years nitrogen macroheterocycles have been widely used as complex-forming agents, membrane active compounds, biologically active substances, and model subjects for theoretical investigations [1]. The little-studied macroheterocyclic compounds containing hydrazine, hydrazone, or hydrazide fragments seemed of definite interest in this scheme [2, 3].

In the present work 16-membered heterocycles (Va-d) containing amide and acylhydrazone fragments have been obtained for the first time starting from 4-substituted 2-acyltosylanilines according to the scheme.

Condensation of (I) with an excess of hydrazine hydrate proceeds significantly more rapidly than with the corresponding ortho-acylanilines where, according to [4], acid catalysis



I—VIII a,d R^1=Br, b R^1=Cl, c R^1=CH_3; a–c R^2=Ph, d R^2=*o*-ClC_6H_4

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TABLE 1. Characteristics of Compounds (II-V), (VII), and (VIII)

Compound	Mp, °C	Found, %					Empirical formula	Calculated, %					Yield, %
		C	H	Hal	N	S		C	H	Hal	N	S	
IIa	175—176	60,2	4,5	18,1	10,4	7,3	$C_{20}H_{18}BrN_3O_2S$	60,1	4,5	18,0	10,5	7,2	76
IIb	180—182	54,0	4,3	8,9	9,4	8,1	$C_{20}H_{18}ClN_3O_2S$	54,1	4,1	8,8	9,5	8,0	74
IIc	150—151	66,5	5,6	—	11,0	8,3	$C_{21}H_{21}N_3O_2S$	66,5	5,6	—	11,0	8,4	80
IId	182—183	50,4	3,7	24,1	8,9	6,8	$C_{20}H_{17}BrClN_3O_2S$	50,2	3,6	24,2	8,8	6,7	78
IIIa	300—301	53,4	3,4	17,0	8,8	6,9	$C_{42}H_{34}Br_2N_6O_6S_2$	53,5	3,6	17,0	8,9	6,8	85
IIIb	295—296	59,0	3,9	8,2	9,9	7,6	$C_{42}H_{34}Cl_2N_6O_6S_2$	59,1	4,0	8,3	9,8	7,5	86
IIIc	268—270	65,0	5,0	—	10,4	7,8	$C_{44}H_{40}N_6O_6S_2$	65,0	4,9	—	10,3	7,9	82
IIId	302—304	50,7	3,3	19,8	8,5	6,5	$C_{42}H_{32}Br_2Cl_2N_6O_6S_2$	50,8	3,2	19,7	8,5	6,4	85
IVa	375—376	53,0	3,4	25,3	13,1	—	$C_{28}H_{22}Br_2N_6O_2$	52,9	3,5	25,2	13,2	—	70
IVb	374—375	61,7	4,02		15,3	—	$C_{28}H_{22}Cl_2N_6O_2$	61,6	4,03	—	15,4	—	68
IVc	326—327	70,0	5,2	—	17,2	—	$C_{29}H_{25}N_6O_2$	71,1	5,1	—	17,2	—	65
IVd	334—335	47,2	4,1	32,5	11,9	—	$C_{28}H_{30}Br_2Cl_2N_6O_2$	47,1	4,2	32,4	11,8	—	75
Va	335—338	52,4	2,9	23,2	12,2	—	$C_{30}H_{20}Br_2N_6O_4$	52,3	2,9	23,2	12,2	—	87
Vb	332—334	60,0	3,2	11,8	13,9	—	$C_{30}H_{20}Cl_2N_6O_4$	60,1	3,3	11,8	14,0	—	90
Vc	340—345	68,9	4,6	—	15,05	—	$C_{32}H_{26}N_6O_4$	68,8	4,6	—	15,05	—	85
Vd	380—385	47,4	2,4	30,4	11,1	—	$C_{30}H_{18}Br_2Cl_2N_6O_4$	47,5	2,4	30,7	11,1	—	86
VIIa	265—267	53,3	3,4	17,1	8,8	6,8	$C_{42}H_{34}Br_2N_6O_6S_2$	53,5	3,6	17,0	8,9	6,8	80
VIIa	370—372	53,1	3,4	25,4	13,0	—	$C_{28}H_{22}Br_2N_6O_2$	52,9	3,5	25,2	13,2	—	30

and extended boiling are required. This is seemingly explained by the fact that introduction of a tosylamino in place of an amino group significantly strengthened the electrophilicity of the carbonyl group of substances (I).

Acylation of (II) with oxalyl chloride proceeded smoothly and compounds (III) were formed in good yield. Detosylation of (III) with concentrated sulfuric acid occurred with partial decomposition but the yields of substances (IV) were sufficiently high and other methods of removing the tosyl group [5] led to lower yields and contaminated products. Condensation of diamines (IV) with oxalyl chloride led to the formation of macroheterocycles (V) in high yield (Table 1).

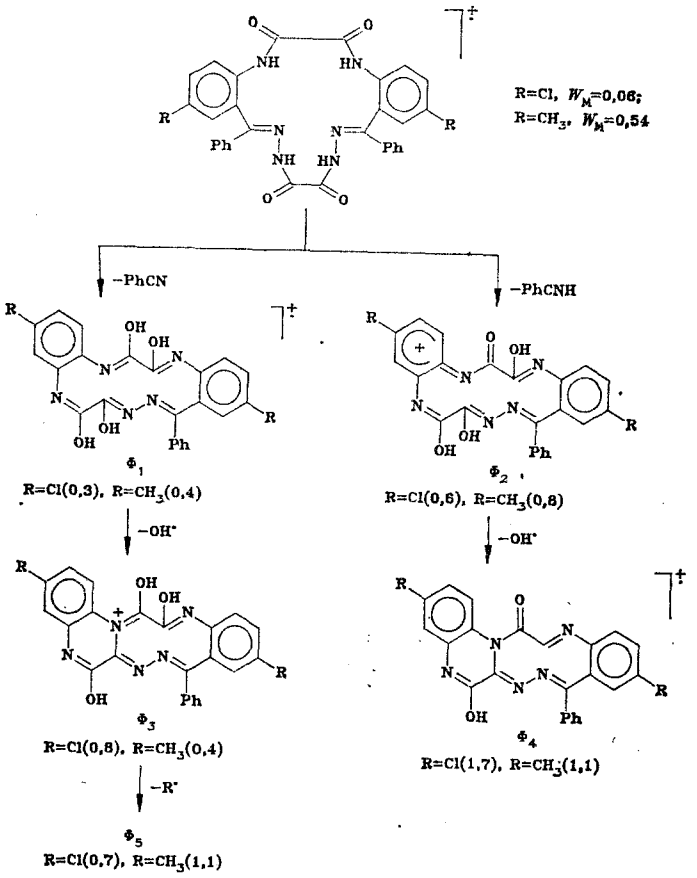
Compound (Va) was synthesized by an alternative synthesis. The corresponding tosylhydrazone (VIa) was obtained by the interaction of 5-bromo-2-aminobenzophenone with tosylhydrazine, and with oxalyl chloride (VIa) gave diamide (VIIa). The latter was detosylated and the resulting dihydrazone (VIIIa) was treated with oxalyl chloride. It should be mentioned that in this particular case the yield of product was lower and working with intermediates was hampered because of low solubility.

The structure of compounds (III) was confirmed by PMR and IR spectroscopy and of (IV) and (V) by IR and mass spectrometry. In the PMR spectrum of compound (IIIa), for example, the chemical shifts of the methyl group protons were observed at 2.3 ppm (6H, s), of amides at 11.6 (1H, s), and 13.0 ppm (1H, s), and of aromatics at 6.6-7.7 ppm (24H, m).

Absorption bands were present in the IR spectra of compounds (III) at 3300-3310 cm^{-1} corresponding to the stretching vibration of NH and also an intense band at 1675-1685 cm^{-1} was assigned to the absorption of carbonyl groups. Compounds (IV) were characterized by an additional set of bands for the stretching vibrations of a primary amide group at 3300-3420 cm^{-1} and split absorption bands were detected for the carbonyl groups at 1700-1720 cm^{-1} besides the NH vibrations (3220-3330 cm^{-1}) for the macroheterocycles (Va-d). The stretching vibrations of C=C and C—H of the aromatic rings appeared at 1600-1620 and 3050-3100 cm^{-1}, respectively.

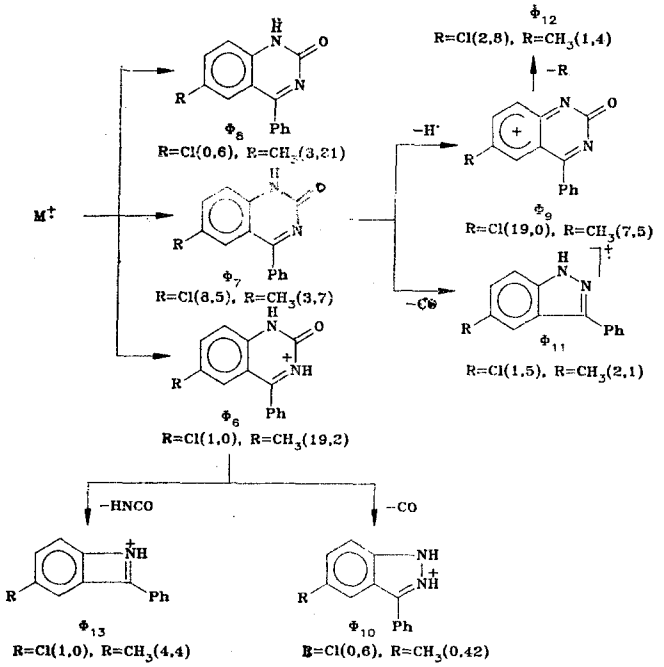
The mass spectra of (Vb,c) were characterized by very low intensity molecular ions which on the one hand eliminate ArCN and ArCNH (ions Φ_1 and Φ_2) and later OH (ions Φ_3 and Φ_4). In addition, the ion Φ_3 eliminated a substituent R' (ion Φ_5). Such a direction of fission is seemingly connected with the inclination of the molecular ion to take the more favorable cyclic structure Φ_3 (anthracene type).

The other direction of fragmentation is determined by the fission of amide and nitrogen-nitrogen bonds with the formation of a series of ions Φ_6-Φ_9 having, evidently, a quinoxaline structure. The formation of benzimidazole structures for ions Φ_{10}, Φ_{11} is also possible as a result of further loss of a molecule of CO by ions Φ_6 and Φ_7 or for ion Φ_{13} as a result of elimination of a molecule of HNCO by ion Φ_6. Loss of the R substituent takes place only from ion Φ_9. The most intense peak in the mass spectrum of (Vc) was ion peak Φ_6 and in the mass spectrum of (Vb) the ion peak Φ_9.



W_m is the stability of the molecular ion (total ion current including all ions to m/z 39).

The peak for the molecular ion was absent from the mass spectrum of (Vd). In the high mass region only low intensity peaks for ions Φ_1 were observed. In addition, halogen containing ions of m/z 634 (Cl_2Br_2), 633 (Cl_2Br_2), 613 ($ClBr_2$), 599 (Cl_2Br_2), and 555 (Cl_2Br) were observed common to both compounds. The latter ion was formed as a result of the loss of an atom of bromine from the ion of m/z 634.



EXPERIMENTAL

IR spectra were taken in KBr disks on a Specord IR-75 spectrophotometer, PMR spectra on a Tesla BS-467 instrument (60 MHz) in $CDCl_3$, internal standard was HMDS, and mass spectra on a Varian MAT-112 instrument at an energy of ionizing electrons of 70 eV and temperatures 30-40°C lower than the melting points of samples.

Compounds (Ia-d) were obtained by the known procedure of [6].

The characteristics of compounds (II)-(VIII) are given in Table 1.

Hydrazones of 5-Substituted 2-Tosylaminobenzophenones (IIa-d). A suspension of (Ia-d) (0.01 mole) in 85% hydrazine hydrate (10 ml) was boiled for 40 min until complete solution. The solution was cooled to room temperature and chloroform (30 ml) added, then the mixture was washed three times with water. The chloroform solution was evaporated at reduced pressure. Hexane and ether were added to the residue. The precipitated crystals were filtered off and recrystallized from methanol.

Oxalylhydrazides of 5-Substituted 2-Tosylaminobenzophenones (IIIa-d). Compounds (IIa-d) (20 mmole) in absolute benzene (30 ml) were heated to boiling and oxalyl chloride (15 mmole) in absolute benzene (5 ml) was added during 30 min. After precipitation of a solid, the mixture was stirred for 1 h and filtered. The solid was washed with ether, with hexane, and recrystallized from chloroform.

Oxalyldihydrazido 5-Substituted 2-Aminobenzophenones (IVa-d). Compounds (IVa-d) (10 mmole) were stirred in concentrated sulfuric acid until complete solution and the mixture left for one day at room temperature. The solution was poured onto ice with vigorous stirring. The product was extracted with chloroform (3 × 50 ml) and the extract washed three times with water. The chloroform solution was evaporated at reduced pressure, the precipitated solid was filtered off, and recrystallized from dioxan.

3,5,14,16-Tetrasubstituted Dibenzo[d,j][1,2,6,9,13,14]hexaazahexadeca-2,4,10,12-tetraene-7,8,15,16-tetraone (Va-d). Oxalyl chloride (15 mmole) in absolute benzene (5 ml) was added during 30 min with stirring to a suspension of (IVa-d) (10 mmole) in absolute benzene and the mixture was boiled for 5 h. The precipitated solid was filtered off, washed with boiling methanol and then with benzene.

Tosylhydrazone of 5-Bromo-2-oxalyldiamidobenzophenone (VIIa). Compound (VIa) (4.44 g) in anhydrous benzene (30 ml) was heated to boiling and oxalyl chloride (0.426 ml) in anhydrous benzene (5 ml) was added during 30 min. After precipitation of a solid the mixture was stirred for 1 h and filtered. The solid was washed with alcohol and with ether, then recrystallized from dioxan, giving product (4 g).

Hydrazone of 5-Bromo-2-oxalyldiamidobenzophenone (VIIIa). Compound (VIIa) (10 mmole) was stirred in concentrated sulfuric acid (20 ml) at room temperature until complete solution and left for one day. The solution was poured onto ice with vigorous stirring. The product was extracted with chloroform (3 × 40 ml) and the extract washed three times with water. The chloroform solution was evaporated under reduced pressure and the precipitated solid was filtered off, washed with alcohol and with benzene.

5,14-Dibromo-3,16-diphenyldibenzo[d,j][1,2,6,9,13,14]hexaazahexadeca-2,4,10,12-tetraene-7,8,15,16-tetraone (Va) was synthesized from (VIIIa) in the same way as from (IVa). The initial tosylhydrazone of 5-bromo-2-aminobenzophenone was obtained in a similar manner from the corresponding hydrazone as in [4].

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