CONDENSED IMIDAZO-1,2,4-AZINES.

9.* IMIDAZO[1,2-b]-1,2,4-TRIAZINE DERIVATIVES IN ELECTROPHILIC SUBSTITUTION REACTIONS

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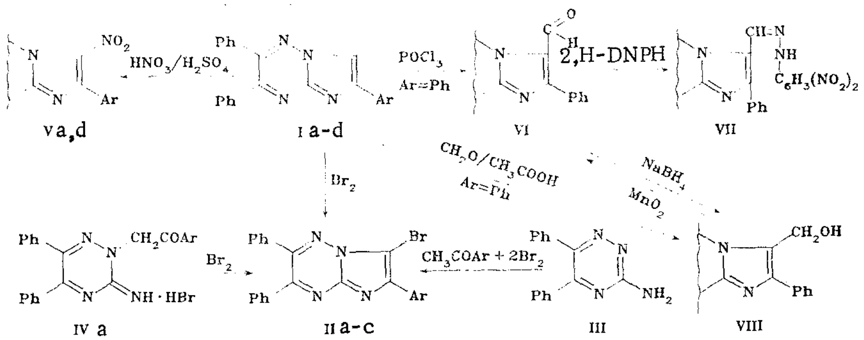
It is shown that, in agreement with the results of quantum-chemical calculations by the CNDO/2 (complete neglect of differential overlap) method, the bromination, nitration, formylation, and hydroxymethylation of 2,3,6-triarylimidazo[1,2-b]-1,2,4-triazines take place at the $C_{(7)}$ atom.

Among imidazo[1,2-b]-1,2,4-triazine derivatives we have detected compounds that have intense luminescence [2] and the ability in solutions and in the vapor state to generate laser emission in the visible region of the spectrum [3, 4]. The present communication is devoted to a study of electrophilic substitution reactions in the imidazo[1,2-b]-1,2,4-triazine series in order to synthesize new efficient lumogens and laser dyes. According to the results of quantum-chemical calculations (see Fig. 1) that we performed by the CNDO/2 (complete neglect of differential overlap) method, the $C_{(7)}$ atom has the highest π-electron surplus character of all of the carbon atoms in the imidazo[1,2-b]-1,2,4-triazine (I) molecule. In this connection, one might have expected increased reactivity of the 7 position in electrophilic substitution reactions.

It is known that imidazole [5, 6] and its condensed systems with a nitorgen atom in common [7-10] react readily with bromine in organic solvents. We therefore also used mild conditions to obtain bromo-substituted imidazo[1,2-b]-1,2,4-triazines. Thus the corresponding 7-bromo derivatives IIa-c were obtained by the action of bromine on 2,3,6-trisubstituted imidazo-1,2,4-triazines Ia-c [11] in dimethylformamide (DMF) at 18-20°C. However, even under these conditions we observed replacement of the chlorine atom by bromine, in addition to bromination of the 7 position, to give IIb in the case of 2,3-diphenyl-6-(p-chlorophenyl)imidazo[1,2-b]-1,2,4-triazine (Id).



I, II, IV, Va Ar=C_6H_5; b Ar=4-BrC_6H_4; c Ar=4-$NO_2C_6H_4$; d Ar=4-ClC_6H_4

Substituted 7-bromoimidazo[1,2-b]-1,2,4-triazines are also formed in the reaction of equimolar amounts of 3-amino-5,6-diphenyl-1,2,4-triazine (III) with acetophenone or p-chloroacetophenone and excess bromine. It should be noted that, as in the bromination of Id, exchange of the chlorine atom for a bromine atom is observed in this case.

Compound IIa was also synthesized as a result of the reaction of 2-benzoylmethyl-3-imino-2,3-dihydro-1,2,4-triazine (IVa) [11] with bromine in acetic acid.

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*See [1] for Communication 8.

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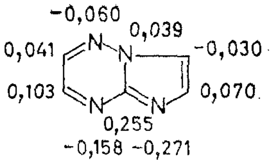

Fig. 1. Magnitudes of the π charges in the imidazo[1,2-b]-1,2,4-triazine molecule calculated by the CNDO/2 method.

The synthesis of 7-bromo derivatives IIa, b from III and IVa evidently proceeds through an intermediate step involving the formation of imidazotriazines Ia, d, which undergo subsequent bromination under the reaction conditions.

The increased electron density on the $C_{(7)}$ atom suggests that the bromine atom in IIa-c will have low lability in nucleophilic substitution reactions. In fact, 7-bromo-substituted IIa-c do not react with reagents such as primary amines, NaSH, and H_2NNH_2 even under severe conditions (on heating to 190-200°C in a sealed ampul).

In contrast to the analogous polycyclic systems that contain an imidazole or pyrrole ring [12-15], in which the phenyl ring also undergoes nitration, 7-nitro derivatives Va, d are formed by the action of fuming nitric acid in concentrated sulfuric acid on 2,3,6-triaryl-substituted imidazo[1,2-b]-1,2,4-triazines Ia, d.

In contrast to the PMR spectra of starting Ia-d, the PMR spectra of products IIa-c and Va, d do not contain signals of an imidazole proton at 7.90-8.00 ppm, which indicates substitution of the 7 position.

7-Formyl dreivative VI was synthesized by the action of the Vilsmeier complex on triphenyl-substituted imidazotriazine Ia. Aldehyde VI forms hydrazone VII in high yield with 2,4-dinitrophenylhydrazine (2,4-DNPH) in acetic acid.

A νCO absorption band at 1690 cm^{-1} is observed in the IR sepctrum of VI. An absorption band associated with the stretching vibrations of an exocyclic C=N bond at 1620 cm^{-1} and a νNH band at 3080 cm^{-1} are characteristic for hydrazone VII.

2,3,6-Triphenyl-6-formylimidazo[1,2-b]-1,2,4-triazine (VI) is reduced to the corresponding 7-hydroxymethyl-substituted VIII by the action of sodium borohydride in anhydrous DMF. Compound VIII is also formed by the direct introduction of a hydroxymethyl group by means of refluxing imidazotriazine IIa in a solution of formaldehyde and acetic acid. Oxidation of alcohol VIII with active manganese dioxide again leads to the formation of aldehyde VI.

A diffuse νOH band at 3280 cm^{-1} appears in the IR spectrum of VIII. In addition to a complex multiplet of aromatic protons at δ 7.16-7.65 ppm and 8.04-8.20 ppm (the ratio of the integral intensities was 10:5, respectively), a singlet of protons of a methylene group with δ 5.00 ppm (2H) is recorded in its PMR spectrum. The molecular mass of VIII found by mass spectrometry corresponds to the calculated value, and the character of the fragmentation confirms the proposed structure. Thus the elimination of hydrogen (m/z 377) and an OH group (m/z 361) directly from the molecular ion (in both cases the β cleavage that is usually observed for alcohols of the benzyl type) characterizes the presence of a CH_2OH group in the molecule. The $[M-H]^+$ and $[M-OH]^+$ ions are probably rearranged ions (standard expansion of the imidazole ring occurs). This facilitates the ejection of a CO particle (ion with m/z 349) in the first case and the splitting out of $CH{\equiv}C{-}C_6H_5$ (ion with m/z 259) in the second case. These fragmentations confirm that the substituents are located in the imidazole part of the molecules.

The appearance in the mass spectrum of alcohol VIII of fragment ions with m/z 178 ($[C_6H_5{-}C{\equiv}C{-}C_6H_5]^{+\cdot}$) and 152 (diphenylene) proves that the phenyl rings are located in the triazine ring. The number of phenyl groups is also monitored satisfactorily by the successive splitting out of C_6H_5CN particles from the $M^{+\cdot}$ and $[M-H]^+$ ions: peaks with m/z 275, 172, and 69 and 274, 171, and 68, respectively.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra were recorded with a Brucker WH-90 spectrometer with tetramethylsilane as the internal standard. The mass spectrum of alcohol VIII was obtained with an LKB-2091 spectrometer. The characteristics of the compounds obtained for the first time are given in Table 1.

TABLE 1. Characteristics of the Compounds Obtained

Compound	mp,[a] °C	R_f (system)[b]	Found, %			Empirical formula	Calc., %			Yield, % (method)
			C	H	N		C	H	N	
IIa	201—202	0,67 (A)	64,4	3,3	13,4	$C_{23}H_{15}BrN_4$[c]	64,7	3,5	13,1	80 (A); 75 (B)
IIb	250—251	0,33 (A)	—	—	11,2	$C_{23}H_{14}Br_2N_4$[d]	—	—	11,1	92 (A); 87 (B)
IIc	290—291	0,82 (B)	58,8	3,1	15,0	$C_{23}H_{14}BrN_5O_2$	58,5	3,0	14,8	94 (A)
Va	262—263	0,69 (B)	—	—	18,0	$C_{23}H_{15}N_5O_2$	—	—	17,8	58
Vd	297—298	0,58 (B)	—	—	16,7	$C_{23}H_{14}ClN_5O_2$[e]	—	—	16,4	62
VI	180—182	0,75 (B)	76,8	4,5	15,0	$C_{24}H_{16}N_4O$	76,6	4,3	14,9	79
VII	276—278	0,81 (B)	64,6	3,3	20,3	$C_{30}H_{20}N_8O_4$	64,8	3,2	20,13	95
VIII	242—244	0,29 (B)	76,4	4,8	14,8	$C_{24}H_{18}N_4O$	76,2	4,8	14,8	82 (A); 84 (B)

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[a] The compounds were purified by crystallization from DMF (IIa-c), acetone (Va, d), aqueous DMF (VI, VIII), and acetic acid (VII). [b] The chromatographic mobilities of the compounds were measured on Silufol plates in DMF—water (5:6) (A), CH OH—butanol—water (21:1:5) (B), and CH_3OH—$CHCl_3$ (C) systems. [c] Found: Br 18.9%. Calculated: Br 18.7%. [d] Found: Br 31.5%. Calculated: Br 31.5%. [e] Found: Cl 8.2%. Calculated: Cl 8.3%.

2,3,6-Triaryl-7-bromoimidazo[1,2-b]-1,2,4-triazines (IIa-c). A) A solution of 3.2 g (20 mmole) of bromine in 10 ml of DMF was added dropwise at 18-20°C to a solution of 10 mmole of the imidazo[1,2-b]-1,2,4-triazine (Ia-d) in 80-120 ml of DMF, and the mixture was stirred for 30 min. The resulting precipitate was removed by filtration and suspended in water. The suspension was neutralized with ammonia and filtered, and the precipitate was dried to give IIa-c. Compound IIa was also formed in 70% yield under similar conditions by the action of bromine on iminotriazine IVa [11].

B) A 3.2-g (20 mmole) sample of bromine was added at 18-20°C to a mixture of 1.24 g (5 mmole) of aminotriazine III and 5.5 mmole of acetophenone (p-chloroacetophenone) in 25 ml of acetic acid, and the mixture was stirred at this temperature for 30 min and at 90°C for another 30 min, after which it was poured into water. The resulting precipitate was removed by filtration and neutralized with $NaHCO_3$ solution. The product was removed by filtration, washed with water, and dried to give IIa, b.

2,3,6-Triaryl-7-nitroimidazo[1,2-b]-1,2,4-triazines (Va, d). A 1.26-g (20 mmole) sample of fuming HNO_3 (sp. gr. 1.56) was added dropwise at 0-2°C to a solution of 10 mmole of imidazotriazine Ia, d in concentrated H_2SO_4, and the mixture was stirred for 2-3 h. It was then poured over ice, and the aqueous mixture was neutralized with $NaHCO_3$ solution. The resulting precipitate was removed by filtration, washed with water, and dried to give Va, d.

2,3,6-Triphenyl-7-formylimidazo[1,2-b]-1,2,4-triazine (VI). A 1.34-g (9 mmole) sample of $POCl_3$ was added with stirring to a solution of 0.7 g (2 mmole) of Ia in 10 ml of anhydrous DMF, and the mixture was maintained at 20-25°C for 1.5 h and at 80°C for 1.5 h. It was then cooled and poured over ice, and the mixture was neutralized with $NaHCO_3$ solution. The resulting precipitate was removed by filtration and washed with water to give formyl derivative VI.

2,4-Dinitrophenylhydrazone VII was obtained by refluxing equimolar amounts of aldehyde VI and 2,4-dinitrophenylhydrazine in acetic acid for 1 h.

2,3,6-Triphenyl-7-hydroxymethylimidazo[1,2-b]-1,2,4-triazine (VIII). A) A 0.08-g (2 mmole) sample of sodium borohydride was added in portions to a solution of 0.38 g (1 mmole) of 7-formyl derivative VI in 15 ml of anhydrous DMF, and the mixture was stirred at 20-22°C for 4 h. It was then poured into 50 ml of water, the excess sodium borohydride was decomposed with 25% sulfuric acid solution, and the precipitated VIII was removed by filtration. Mass spectrum, m/z (relative intensities in percent): 379 (27.3), 378 (100), 377 (15.5), 363 (10.2), 362 (22.8), 361 (97.5), 349 (15.7), 275 (10.5), 274 (16.7), 259 (17.9), 258 (32.6), 246 (20.9), 190 (7.6), 180 (12.8), 179 (7.5), 178 (33.7), 176 (4.2), 172 (14.2), 171 (7.9), 165 (11.4), 156 (8.4), 155 (36.3), 152 (4.0), 144 (5.5), 143 (11.1), 130 (10.3), 129 (16.0), 128 (31.6), 117 (7.2), 116 (26.8), 115 (22.6), 114 (10.8), 105 (8.0), 104 (38.3), 103 (44.2), 102 (44.2), 101 (14.6), 89 (20.4), 88 (7.5), 78 (5.1), 77 (38.3), 76 (10.7), 69 (4.3), 68 (3.2), 63 (6.3), 52 (4.0), 51 (10.3), 44 (5.8), 41 (5.0), 40 (13.9).

B) A mixture of 0.69 g (2 mmole) of Ia and 10 ml of formalin in 20 ml of glacial CH_3COOH was refluxed for 2 h, after which it was cooled, and the precipitated alcohol VIII was removed by filtration, washed with water, and dried.

Oxidation of 7-Hydroxymethyl-2,3,6-triphenylimidazo[1,2-b]-1,2,4-triazine (VIII). A 2.5-g (29 mmole) sample of freshly prepared active MnO_2 was added in portions to a solution of 0.76 g (2 mmole) of alcohol VIII in 100 ml of anhydrous chloroform, and the mixture was stirred at 18-20°C for 36 h and refluxed for 30 min. The precipitated manganese was removed by filtration, half of the chloroform was removed by vacuum distillation, and the resulting precipitate was removed by filtration to give 0.46 g (61%) of aldehyde VI.

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