PREPARATION AND BIOLOGICAL ACTIVITY OF 2-ARYLIMINO DERIVATIVES OF N-METHYL POLYMETHYLENEIMINES

A. M. Zhidkova, V. G. Granik,
N. S. Kuryatov, V. P. Pakhomov,
R. G. Glushkov, and B. A. Medvedev

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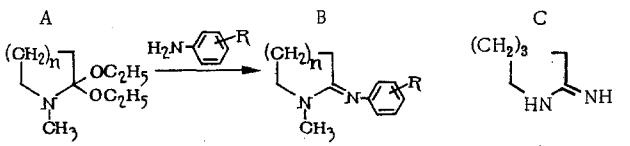
A number of papers have appeared during the last few years in which attention is directed to the high biological activity of compounds containing the amidine grouping [1, 2, 3]. The object of the present investigation was to prepare a series of compounds of this type (IV-VI) (see Table 1) from a group of lactam acetals (I-III), and to correlate the structure of these products with their pharmacological activity.

Attempts to condense the diethylacetals of the N-methyl derivatives of butyro-, valero-, and caprolactams [(I), (II), and (III), respectively] with appropriate aromatic amines revealed that the temperature requisite for these reactions differed from case to case, i.e., that the velocities of the reactions were considerably affected not only by the size of the lactam ring in (I)-(III) but also by the nature of the R group of the amine reacting therewith. The comparative reactivity of the three lactam acetals was determined by subjecting them to competitive reaction with one of the amines, viz., with p-nitroaniline (R = p-NO_2), and establishing the proportion of the products, (IVa), (Va), and (VIa) respectively, so formed. The results obtained, followed by means of gas–liquid chromatography, showed that the compounds were produced in the proportions 18:1:8.3, respectively. This conforms with the classical view of the relationship between reactivity and ring size, and agrees well with the H. C. Brown I-strain concept (see Gol'dfarb and Belen'kii [4]). It indicates that an orbital $sp^3 \rightarrow sp^2$ jump occurs during the velocity-determining phase of the reaction resulting from an alteration of configuration at the receptor center and attended by a decrease in unbonded interaction at that point. Such a decrease would be more pronounced in five- and seven-membered rings than in the hexacyclic case.



(I) (n = 1)
(II) (n = 2)
(III) (n = 3)

(IVa) (n = 1; R = p-NO_2)
(IVb) (n = 1; R = p-OCH_3)
(IVc) (n = 1; R = p-Cl)
(Va) (n = 2; R = p-NO_2)
(Vb) (n = 2; R = p-OCH_3)
(Vc) (n = 2; R = p-Cl)
(VIa) (n = 3; R = p-NO_2)
(VIb) (n = 3; R = p-OCH_3)
(VIc) (n = 3; R = p-Cl)
(VId) (n = 3; R = m-NO_2)
(VIe) (n = 3; R = m-F)

(VII)

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow.
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TABLE 1. 2-Arylimino Derivatives of N-Methyl Polymethyleneimines

Compound	Yield, %	Reaction temp., °C	Duration of reaction, h	bp, °C	mp, °C*	n_D^{20}	Found, %				Empirical formula	Calc., %			
							C	H	Cl	N		C	H	Cl	N
IVa	82	60	1,5	—	70—1	—	60,38	6,04	—	19,17	$C_{11}H_{13}N_3O_2$	60,27	5,93	—	19,13
IVb	79	60	1	163—4 (5 mm)	—	1,5876	70,51	7,87	—	—	$C_{12}H_{16}N_2O$	70,59	7,84	—	—
IVc	45	60	1	140—1 (3 mm)	—	1,5991	63,36	6,22	—	—	$C_{11}H_{13}ClN_2$	63,31	6,24	—	—
IVc·HCl	—	—	—	—	267—8	—	—	—	28,16	11,45	$C_{11}H_{13}ClN_2 \cdot HCl$	—	—	28,57	11,43
Va	87	60	1	—	72—3	—	61,80	6,52	—	—	$C_{12}H_{15}N_3O_2$	61,80	6,44	—	—
Vb	81	60	1,5	—	76—6,5	—	71,74	8,26	—	—	$C_{13}H_{18}N_2O$	71,56	8,26	—	—
Vc	80	40	2	153—4 (4 mm)	—	1,5966	64,85	6,78	—	—	$C_{12}H_{15}ClN_2$	64,72	6,74	—	—
Vc·HCl	—	—	—	—	285—6	—	—	—	27,24	10,86	$C_{12}H_{15}ClN_2 \cdot HCl$	—	—	27,41	10,81
VIa·HCl	—	—	—	—	244—5	—	—	—	12,49	15,03	$C_{13}H_{17}N_3O_2 \cdot HCl$	—	—	12,54	14,84
VIb·HCl	—	—	—	—	162—3	—	—	—	12,57	10,36	$C_{14}H_{20}N_2O \cdot HCl$	—	—	13,22	10,43
VIc·HCl	—	—	—	—	228—9	—	—	—	25,99	10,14	$C_{13}H_{17}ClN_2 \cdot HCl$	—	—	26,01	10,25
VId	86	35	5	194—6 (1 mm)	—	—	63,20	6,98	—	16,83	$C_{13}H_{17}N_3O_2$	63,16	6,88	—	17,00
VId·HCl	—	—	—	—	203—5	—	—	—	12,32	14,74	$C_{13}H_{17}N_3O_2 \cdot HCl$	—	—	12,52	14,82
VIe·HCl	—	—	—	—	177,0—7,5	—	60,92	7,14	13,98	11,23	$C_{13}H_{17}FN_2 \cdot HCl$†	60,78	7,02	13,81	10,92

*Compounds (IVa), (Va), (Vb) were crystallized from hexane; (IVc),HCl and (Vc),HCl from ethanol–acetone (1:1); (VId),HCl from ethanol–acetone (1:3); (VIa),HCl from propanol; (VIb),HCl and (VIe),HCl from acetone; (VIc),HCl from acetone–propanol (20:7).

†Found, %: F 7.27; calculated, %: F 7.41.

Another competitive-reaction experiment, set up this time with a single lactam acetal [viz. (III)] and the two amines, p-anisidine and p-nitroaniline (R = p-OCH_3 and p-NO_2, respectively), proved that the reaction occurred only with the more strongly basic amine.

The pharmacological activity of the eleven compounds prepared by means of this reaction (see Table 1) was compared with that of the n = 3 progenitor of the series, 2-iminohexamethyleneimine ("caprolactimamidine") (VII), which was obtained by known methods [5]. (The work was carried out in the Pharmacology Department of this Institute.) The hydrochloride of (VII) has adrenomimetic properties; these are manifested in the experimental animal by vasoconstriction, arterial pressor action, erection of the hair, and contraction of the nictitating membrane. While the ganglion-blocking agent, hexonium, is merely able to reduce the resulting hypertension and decrease the extent of the nictitating membrane contraction, the adrenolytic drug, tropaphen, annuls the various effects altogether. It would appear therefore that the adrenomimetic effects of (VII) are produced, at least in part, by stimulation of sympathetic ganglia and related structures. On passing, however, to the hydrochlorides of (IVc), (Vc), and the five n = 3 compounds, (VIa, b, c, d, and e), the adrenomimetic properties of (VII) are entirely replaced by nicotiniform effects. Thus, the hypertension, respiratory stimulation, and nictitating membrane contraction, elicitated by these seven compounds at ordinary dose levels, are inhibited by ganglion-blocking agents; at higher dose levels, however, just as in the case of nicotine itself, a two-phase action supervenes, and the stimulus effects initially produced are gradually reversed by ganglion blockade and a set of contrary manifestations finally predominates Among the five n = 3 compounds, (VIa, b, c, d, and e), these nicotiniform properties are most highly pronounced in the case of (VIc) which can elicit such effects in doses of 0.5-2.0 mg kg. Replacement of its p-chloro group by NO_2, to give (VIa), results in decrease in activity, while the exchange of p-Cl by p-OMe leads to a compound, (VIb), which is inactive for all practical purposes. The m-nitro derivative (VId) is, in comparative order of magnitude, less active than its p-isomer (VIa), while the m-fluoro compound (VIe) has half the activity of the p-chloro compound, (VIc). Finally, as to the effect of ring size on nicotiniform activity, the smaller the ring (i.e., the fewer the number of methylene-group members) the more highly active is the compound. Thus, among the p-chlorophenyl derivatives (i.e., the c cases) the order of magnitude is [(IVc); (n = 1)] > [(Vc); (n = 2)] > [(VIc); (n = 3)].

EXPERIMENTAL

2-Arylimino-N-methylpolymethyleneimines (IVa), (IVc), (Va), and (VId). These compounds were obtained by the method previously described [6]. Their hydrochlorides were prepared by treating ethereal solutions of the bases with an ethanolic solution of hydrogen chloride. Reaction conditions and constants of the resulting products are given in Table 1. The two competitive reactions were carried out at room temperature; in the first, in which the three lactam acetals, (I), (II), and (III), were reacted with p-nitroaniline, the lactam acetals were used in large excess: in the other, in which lactam acetal (III) was reacted with the amines p-nitroaniline and p-anisidine, the amines were in large excess. Controls were effected by means of gas–liquid chromatography using a JGC-810 outfit and a flame-ionization detector. The dimensions of the column were 60 × 0.3 cm, and the stationary phase, 1% SE-30 and 1% OV-17, was on chromosorb W. The current rate of the gel was 50 ml/min under isothermic conditions (190°). The relative retention times for (IVc), (VC), and (VIc) were in the proportions 1 : 1.42 : 2.02.

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