INVESTIGATION OF 2,3-POLYMETHYLENEQUINOLINES

IX.* ARYLHYDRAZIDES OF 1,2,3,4-TETRAHYDROACRIDINE-9-CARBOXYLIC AND 2,3-PENTAMETHYLENEQUINOLINE-4-CARBOXYLIC ACIDS

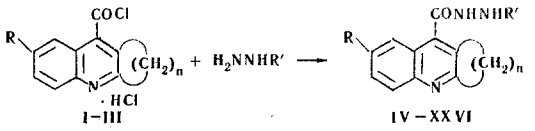
M. E. Konshin and É. S. Abramochkin

UDC 547.831

The arylhydrazides of 1,2,3,4-tetrahydroacridine-9-carboxylic and 2,3-pentamethylene-quinoline-4-carboxylic acids were obtained by the reaction of the hydrochlorides of the acid chlorides of these acids with arylhydrazines. Their properties and biological activity were investigated.

Hydrazides of isonicotinic acid have been recommended as valuable medicinal preparations [2,3]. Analogs of isonicotinic acid hydrazide in the quinoline and acridine series have been investigated [4]. The hydrazides of 2,3-polymethylenequinoline-4-carboxylic acid are unknown.

In the present paper, we describe the synthesis of arylhydrazides of 1,2,3,4-tetrahydroacridine-9-carboxylic and 2,3-pentamethylenequinoline-4-carboxylic acids via the scheme



*See [1] for communication VIII.

TABLE 1. Arylhydrazides of 2,3-Polymethylenequinoline-4-carboxylic Acids (IV-XXVI)

Comp.	R	R′	n	mp, °C (from alcohol)	Empirical form.	N, % found	N, % calc.	Yield, %
IV	H	C_6H_5	4	212—214	$C_{20}H_{19}N_3O$	13,5	13,2	50
V	H	p-$CH_3C_6H_4$	4	215	$C_{21}H_{21}N_3O$	12,6	12,7	30
VI	H	p-BrC_6H_4	4	232—234	$C_{20}H_{18}BrN_3O$	10,2	10,6	45
VII	H	o-BrC_6H_4	4	205—207	$C_{20}H_{18}BrN_3O$	10,9	10,6	40
VIII	H	m-ClC_6H_4	4	206—207	$C_{20}H_{18}ClN_3O$	11,7	12,0	42
IX	H	o-ClC_6H_4	4	209—210	$C_{20}H_{18}ClN_3O$	11,8	12,0	48
X	H	C_6H_5	5	218—219	$C_{21}H_{21}N_3O$	12,8	12,7	80
XI	H	p-$CH_3C_6H_4$	5	216—217	$C_{22}H_{23}N_3O$	12,2	12,2	79
XII	H	o-$CH_3C_6H_4$	5	205—206	$C_{22}H_{23}N_3O$	12,3	12,2	74
XIII	H	m-$CH_3C_6H_4$	5	197—198	$C_{22}H_{23}N_3O$	12,3	12,2	80
XIV	H	p-ClC_6H_4	5	239—240	$C_{21}H_{20}ClN_3O$	11,7	11,5	82
XV	H	m-ClC_6H_4	5	206—207	$C_{21}H_{20}ClN_3O$	11,6	11,5	79
XVI	H	o-ClC_6H_4	5	225—226	$C_{21}H_{20}ClN_3O$	11,7	11,5	74
XVII	H	p-BrC_6H_4	5	244—245	$C_{21}H_{20}BrN_3O$	10,0	10,2	78
XVIII	H	o-BrC_6H_4	5	212—213	$C_{21}H_{20}BrN_3O$	10,3	10,2	69
XIX	CH_3	C_6H_5	5	199—201	$C_{22}H_{23}N_3O$	12,1	12,2	78
XX	CH_3	o-$CH_3C_6H_4$	5	242—243	$C_{23}H_{25}N_3O$	11,4	11,7	68
XXI	CH_3	m-$CH_3C_6H_4$	5	214—215	$C_{23}H_{25}N_3O$	11,7	11,7	81
XXII	CH_3	p-ClC_6H_4	5	213—214	$C_{22}H_{22}ClN_3O$	11,1	11,1	80
XXIII	CH_3	m-ClC_6H_4	5	228—229	$C_{22}H_{22}ClN_3O$	11,0	11,1	78
XXIV	CH_3	o-ClC_6H_4	5	232—233	$C_{22}H_{22}ClN_3O$	11,1	11,1	72
XXV	CH_3	p-BrC_6H_4	5	225—226	$C_{22}H_{22}BrN_3O$	10,1	9,9	76
XXVI	CH_3	o-BrC_6H_4	5	223—224	$C_{22}H_{22}BrN_3O$	10,1	9,9	69

Perm Pharmaceutical Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 546-547, April, 1972. Original article submitted December 3, 1970.

The arylhydrazides of 1,2,3,4-tetrahydroacridine-9-carboxylic (IV-IX) and 2,3-pentamethylenequinoline-4-carboxylic (X-XXVI) acids (Table 1) were obtained by the reaction of the hydrochlorides of the acid chlorides of 1,2,3,4-tetrahydroacridine-9-carboxylic (I), 2,3-pentamethylenequinoline-4-carboxylic (II), and 6-methyl-2,3-pentamethylenequinoline-4-carboxylic (III) acids, previously described in [1,5], with arylhydrazines.

The best results were obtained when the reaction was carried out in benzene with an acid chloride to arylhydrazine ratio of 1 : 1 in the presence of triethylamine as an acid-binding agent. When the reaction is carried out in pyridine and when excess arylhydrazine is added, pronounced resinification is observed, which hinders isolation of the reaction product.

Refluxing methyl 1,2,3,4-tetrahydroacridine-9-carboxylate with arylhydrazines in various solvents (alcohol, benzene, isoamyl alcohol) did not give arylhydrazides. This may be explained by the lower reactivity of the ester as compared with the acid chloride.

Arylhydrazides IV-XXVI, which are colorless, crystalline substances with high melting points, have basic character and form hydrochlorides.

A pharmacological investigation of IV-VI, VIII-X, XII-XVI, and XXIII-XXV was performed.* These compounds have low toxicity: LD_{50} for intraperitoneal injection is 400-1500 mg/kg and higher. Rather strongly pronounced anticurare activity is observed only for XIII. Compounds XVI and XXIV display synergism with ditiline.

EXPERIMENTAL

Arylhydrazides of 1,2,3,4-Tetrahydroacridine-9-carboxylic Acids (IV-IX). A 0.01-mole sample of the arylhydrazine was dissolved in a mixture of 15 ml of benzene and 4 ml of triethylamine. A total of 0.01 mole of the hydrochloride of the acid chloride of 1,2,3,4-tetrahydroacridine-9-carboxylic acid was added to the resulting solution, and the mixture was heated on a water bath for 1 h. The resulting precipitate was removed by filtration and washed with water and 10% sodium carbonate solution.

Arylhydrazides of 2,3-Pentamethylenequinoline-4-carboxylic Acid (X-XXVI). These compounds were similarly obtained. At the end of the reaction, the precipitated triethylamine hydrochloride was removed by filtration. The benzene solution was washed with water, and a portion of the benzene was removed by distillation. The solution was cooled to give a crystalline precipitate of reaction product, which was worked up in the usual manner.

LITERATURE CITED

1. É. S. Abramochkin, M. E. Konshin, A. S. Zaks, and L. G. Zil'bermints, Khim.-Farmats. Zh. (1972, in press).
2. M. N. Shchukina, Zh. Vses. Khim. Obshchestva, 10, 637 (1965).
3. M. D. Mashkovskii, Zh. Vses. Khim. Obshchestva, 9, 433 (1964).
4. A. Spasov and M. Atanasova, Nauchn. Trudy Vyssh. Med. Inst., Sofiya, 39, 267 (1960); Ref. Zh. Khim., 18Zh201 (1962).
5. O. Yu. Magidson and A. I. Travin, Zh. Obshch. Khim., 7, 842 (1937).

*The tests were performed by A. S. Zaks and L. D. Zil'bermints, to whom the authors express their thanks.