AMINOACETYLENIC CARBONYL COMPOUNDS.

I. 2-SUBSTITUTED 2-(δ-AMINOBUTYNYL)-1,3-INDANDIONES

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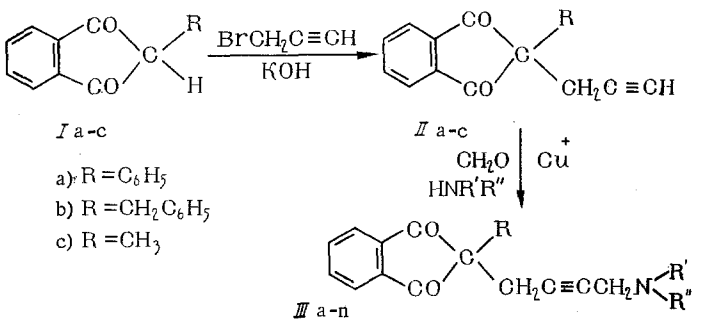
Aminoacetylenic carbonyl compounds have been little studied [1]. They merit attention for their polyfunctionality, as well as for their potential pharmacological activity. Many observations have been accumulated on the pharmacological activity of aminoacetylenes [2-5]. On the other hand, aminocarboxylic and dicarboxylic compounds are also characterized by a wide spectrum of activity on the central nervous system [6].

In the present investigation we studied the possibility of synthesizing aminoacetylenic derivatives of the indandione series. Alkylation of 2-substituted indan-1,3-diones (Ia-Ic) with propargyl bromide (best in the presence of sodium iodide) yielded 2-substituted 2-propargylindan-1,3-diones (IIa-IIc). The structures of IIa-IIc were confirmed by IR spectra (Table 1) and by study of their chemical properties. In the IR spectra of IIa-IIc one finds the characteristic twin absorption maxima for the dicarbonyl grouping in the 1707-1754 cm^{-1} interval [7] and absorption maxima at the frequencies of monosubstituted acetylenes: ν ≡C-H 3258–3295 cm^{-1}, ν C ≡ C 2120–2127 cm^{-1} [8].

Compounds IIa-IIc, as monosubstituted acetylenes, are aminomethylated with paraformaldehyde and secondary amines in dioxane solution in the presence of cuprous acetate:



The structures of the resulting 2-substituted 2-(δ-aminobutynyl)indan-1,3-diones (IIIa-IIIn) were confirmed by IR absorption spectra (Table 2), in which one observes the frequencies characteristic of β-dicarbonyl groups, and of the C≡C bond in disubstituted acetylenes.

TABLE 1. 2-Substituted 2-Propargylindan-1,3-diones (IIa-IIc)

Compound	Yield (%)	Mp (°C)	Empirical formula	Found (%)		Calc. (%)		$\nu_{C=O}$	$\nu_{C\equiv C}$	$\nu_{\equiv C-H}$
				C	H	C	H	cm^{-1}		
IIa	80	136—7	$C_{18}H_{12}O_2$	83,46	4,71	83,06	4,65	1 741(57) 1 707(79)	2 127(57)	3 295(70)
IIb	76	123—124,5	$C_{19}H_{14}O_2$	83,49	5,22	83,19	5,14	1 748(48) 1 709(60)	2 120(34)	3 292(93)
IIc	44	91—2	$C_{13}H_{10}O_2$	78,72	4,92	78,77	5,09	1 754(71) 1 713(93)	2 126(30)	3 258(75)

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TABLE 2. 2-Substituted 2- (δ-Aminobutynyl)indan-1,3-diones (IIIa-IIIn) and Their Hydrochlorides

Compound	Yield (%)	Mp (°)	Found (%)		Empirical formula	Calc. (%)		$\nu_{C=O}$	$\nu_{C\equiv C}$
			Cl	N		Cl	N	cm^{-1}	
IIIa·HCl	65	186—8	10,16	4,08	$C_{24}H_{20}ClNO_2$	10,02	3,96	1 733(56)	
								1 701(86)	2 234(36)
IIIb	96	76—7		3,92	$C_{23}H_{23}NO_2$		4,06		
								1 744(58)	
IIIb·HCl	68	183—5	9,26	3,61	$C_{23}H_{24}ClNO_2$	9,2	3,67	1 706(79)	2 226(22)
IIIc	98	106—7		4,08	$C_{24}H_{23}NO_2$		3,92		
								1 744(34)	
IIIc·HCl	79	203,5—205	9,05	3,71	$C_{24}H_{24}ClNO_2$	9,00	3,56	1 711(70)	2 257(32)
IIId	97	107—8		3,99	$C_{23}H_{21}NO_3$		3,90		
								1 741(36)	
IIId·HCl	74	195—6	8,99	3,54	$C_{23}H_{22}ClNO_3$	8,96	3,54	1 708(67)	2 254(46)
IIIe	96	77—8		3,85	$C_{23}H_{21}NO_2$		4,08		
IIIe·HCl	64	131—3	9,39	3,92	$C_{23}H_{22}ClNO_2$	9,33	3,69	1 732(28)	
								1 695(63)	2 247(27)
IIIf	96	71—2		3,64	$C_{25}H_{27}NO_2$		3,75		
								1 738(48)	
IIIf·HCl	68	174—6	8,67	3,57	$C_{25}H_{28}ClNO_2$	8,65	3,42	1 701(77)	2 240(45)
IIIg·HCl	61	135—7	8,20	3,44	$C_{27}H_{32}ClNO_2$	8,10	3,20	1 744(37)	
								1 704(67)	2 244(44)
IIIh	95	105—7		4,20	$C_{22}H_{21}NO_2$		4,23		
								1 742(64)	
IIIh·HCl	51	191—2	9,64	3,66	$C_{22}H_{22}ClNO_2$	9,64	3,81	1 703(78)	2 240(31)
IIIi	95	95—6		4,07	$C_{24}H_{25}NO_2$		3,90		
								1 736(38)	
IIIi·HCl	68	181—3	8,84	3,39	$CC_{24}H_{26}ClNO_2$	8,96	3,54	1 700(52)	2 237(68)
IIIj	96	115—6		3,72	$C_{25}H_{25}NO_2$		3,77		
								1 735(48)	
IIIj·HCl	74	191—2	8,86	3,25	$C_{25}H_{26}ClNO_2$	8,69	3,43	1 700(64)	2 229(78)
IIIk	97	138—139,5		3,71	$C_{24}H_{23}NO_3$		3,75		
								1 738(55)	
IIIk·HCl	75	176—7	8,82	3,54	$C_{24}H_{24}ClNO_3$	8,65	3,42	1 703(78)	2 244(33)
								1 750(32)	
IIIl·HCl	64	134—135,5	10,89	4,46	$C_{18}H_{22}ClNO_2$	11,09	4,38	1 713(45)	2 213(72)
IIIm	96	46—7		4,63	$C_{19}H_{21}NO_2$		4,74		
								1 748(46)	
IIImHCl	65	170—1	10,69	4,22	$C_{19}H_{22}ClNO_2$	10,70	4,18	1 711(80)	2 227(60)
IIIn	95	79—80		4,78	$C_{28}H_{19}NO_3$		4,71		
IIIn·HCl	62	184—5	10,71	4,33	$C_{18}H_{20}ClNO_3$	10,62	4,20	1 747(60)	
								1 706(84)	2 227(66)

The pharmacological activity of 2-substituted 2-(δ-aminobutynyl)indan-1,3-diones (IIIa-IIIn) was studied in white mice. In all experiments the compound under study was introduced intraperitoneally about 30 min before testing. We studied anti-convulsive activity in relation to maximum electric shock and tranquillizer activity by the rotating rod test. We studied the ability of each substance to intensify hexenal narcosis (hexenal was introduced intravenously in 70 mg/kg doses). We also studied the effect of these compounds on animal behavior and on acute toxicity.

The experimental material was treated statistically by the method of Litchfield and Wilcoxon [9]. In all cases we calculated the median lethal dose (LD_{50}) and the median effective dose (ED_{50}) in proportion to the maximum electric shock and disturbance of coordination of movement, and also the index of intensification of hexenal narcosis (the ratio of narcosis duration in experimental animals to that in the control animals). See Table 3.

From the data in Table 3, it follows that the anticonvulsive activity is most evident in compounds containing the phenyl group (IIIa-IIIg). When the phenyl radical is replaced by benzyl (IIIh-IIIk) or methyl (IIIl-IIIn), some anticonvulsive activity is observed only in compounds containing the morpholine ring (IIIk and IIIn). The remaining compounds have anticonvulsive activity only in doses which exceed one-third of the lethal dose.

All the substances studied have tranquillizer properties; they show disturbance in coordination of movement, and intensify hexenal narcosis. The tranquillizer properties are intensified with increasing chain length of the aliphatic radicals.

It was shown that, in small doses, all the substances studied depress spontaneous motor activity, and at toxic concentrations show motor excitation and tonic-clonic spasms which sometimes terminate in death. Increase in the length of the aliphatic chain on the nitrogen atom reduces toxicity. Reduction in

TABLE 3. Pharmacological Activity of 2-Substituted 2-(δ-Aminobutynyl)indan-1,3-diones (III). The values in parentheses show the confidence limits at P = 0.05

Compound III · HCl	R	R′	R″	LD_{50}	Rotating rod, ED_{50}	Max. electric shock ED_{50}	I, intensification of hexenal narcosis
				in mg/kg			
IIIa	C_6H_5	CH_3	CH_3	68 (53÷87)	30 (26÷35)	—	—
IIIb	C_6H_5	C_2H_5	C_2H_5	65 (46÷81)	25 (19÷31)	22 (20÷25)	2,8
IIIc	C_6H_5	$(CH_2)_5$		94 (84÷104)	65 (55÷77)	36 (33÷40)	2,7
IIId	C_6H_5	$(CH_2)_2$-O-$(CH_2)_2$		240 (170÷336)	64 (56÷73)	—	2,7
IIIe	C_6H_5	$(CH_2)_4$		94 (87÷102)	24 (19÷30)	29 (25÷34)	2,2
IIIf	C_6H_5	$CH(CH_3)_2$	$CH(CH_3)_2$	127 (83÷193)	29 (23÷37)	29 (21÷41)	3,2
IIIg	C_6H_5	C_4H_9	C_4H_9	380 (337÷440)	31 (22÷43)	82 (73÷93)	3,5
IIIh	$CH_2C_6H_5$	CH_3	CH_3	60 (52÷69)	15 (11÷20)	—	2,2
IIIi	$CH_2C_6H_5$	C_2H_5	C_2H_5	73 (62÷68)	19 (15÷24)	—	3,4
IIIj	$CH_2C_6H_5$	$(CH_2)_5$		118 (107÷130)	35 (27÷46)	—	1,7
IIIk	$CH_2C_6H_5$	$(CH_2)_2$-O-$(CH_2)_2$		392 (316÷487)	52 (33÷83)	—	2,3
IIIl	CH_3	C_2H_5	C_2H_5	123 (114÷132)	42 (28÷62)	—	1,7
IIIm	CH_3	$(CH_2)_5$		154 (142÷168)	34 (28÷42)	—	3,6
IIIn	CH_3	$(CH_2)_2$-O-$(CH_2)_2$		820 (710÷947)	125 (106÷148)	—	1,9

toxicity is also observed when the phenyl radical is replaced by benzyl or methyl. The least toxic compounds IIIk and IIIn contain the morpholine group.

From the data given it is apparent that 2-substituted 2-(δ-aminobutynyl)indan-1,3-diones have a depressing effect on the central nervous system.

EXPERIMENTAL

2-Substituted 2-Propargylindan-1,3-diones (IIa-IIc). To a solution of 0.02 mole of a 2-substituted 1,3-indandione (I) and 0.02 mole of potassium hydroxide in 50 ml of ethanol was added 1.65 ml (0.021 mole) of propargyl bromide and 0.2 g of potassium iodide. The mixture was boiled on a water bath until the solution was decolorized. After cooling, the mixture was poured into 200 ml of water. The next day the precipitate was filtered off and recrystallized from ethanol to yield 2-substituted 2-propargylindan-1,3-diones (II). The yield and properties are given in Table 1.

2-Substituted 2-(δ-Aminobutynyl)indan-1,3-diones (IIIa-IIIn). To a solution of 0.01 mole of II in 30 ml of dry dioxane was added 0.015 mole of a secondary amine, 0.03 mole of paraformaldehyde and 0.2 g of cuprous acetate (in the case of dimethylamine the dioxane solution was saturated with dry dimethylamine). The mixture was boiled under reflux for three hours (in the case of dimethylamine the mixture was kept in the boiling water bath in sealed ampoules). After cooling the contents of the flask or ampoule was poured into 150 ml of water. After a day the precipitate (or oil) was separated, washed with water and dissolved in ether. The ether solution was dried over anhydrous magnesium sulfate, filtered, and the filtrate saturated with dry hydrogen chloride. The hydrochloride precipitate was crystallized from a mixture of absolute alcohol and ether. The yields and properties of the resulting hydrochlorides of 2-substituted 2-(δ-aminobutynyl)indan-1,3-diones (III · HCl) are given in Table 2.

An aqueous solution of III · HCl was cooled and stirred while a 20% aqueous ammonia solution was added until a neutral reaction was obtained, and the precipitate removed. The precipitate was the 2-substituted 2-(δ-aminobutynyl)indan-1,3-dione (III) which was readily recrystallized from ethanol. The yields and properties of these compounds are also given in Table 2.

CONCLUSION

2-Substituted 2-propargylindan-1,3-diones were prepared by treating the salt of 2-substituted 1,3-indandione with propargyl bromide. Aminomethylation of the product with paraformaldehyde and secondary amines afforded a series of 2-substituted 2-(δ-aminobutynyl)indan-1,3-diones which exhibit depressant effects on the central nervous system.

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