CHEMISTRY OF OXALYL DERIVATIVES OF METHYL KETONES

XIX. SYNTHESIS AND BIOLOGICAL ACTIVITY OF 5-PHENACYLIDENYL-TETRAHYDROIMIDAZOLE-2,4-DIONES

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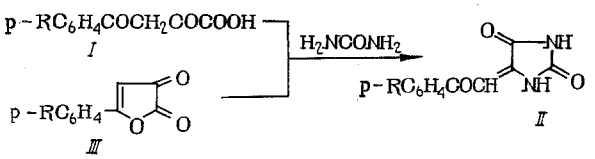
The anticonvulsant properties of 5,5-disubstituted tetrahydroimidazole-2,4-diones are well known: The sodium salt of 5,5-diphenyltetrahydroimidazole-2,4-dione (Difenin) is used for the treatment of epilepsy. We have shown earlier that heterocyclic compounds having phenacylidene substituents possess physiological activity [1-3]. In a search for compounds possessing anticonvulsive activity (ACA), we attempted the synthesis of tetrahydroimidazoles bearing the phenacylidene substituent. Our synthesis involved the reaction of aroylpyruvic acid (I) with urea.

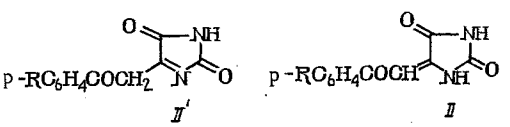
As a result of the low nucleophilicity of urea compared with aromatic amines, its interaction with aroylpyruvic acids (I) required quite stringent conditions (120-130°C, 1.5 h). The reaction products were found to include the desired 5-phenacylidenyltetrahydroimidazole-2,4-diones (II).



R=H, CH_3, CH_3O, Br etc.

Under milder conditions (100-110°C, 20 min), these compounds were formed from 5-arylfuran-2,3-diones (III). The compounds synthesized are given in Table 1.

The tetrahydroimidazole derivatives obtained may exist in the form of two isomeric structures:



In the IR spectra of these compounds, vibrations of the carbonyl in position 2 appear in the 1760-1740 cm^{-1} region (the literature gives 1730 cm^{-1} [4]), absorption in the 1790-1782 cm^{-1} region is consistent with vibrations of the carbonyl in position 4 (the literature gives 1830-1780 cm^{-1} [4]), and the frequency of 1670 cm^{-1} corresponds to the absorption of the side-chain carbonyl.

From the IR spectra, it is difficult to conclude which of the two alternative structures is actually present, since the spectral readings in mineral oil show only broad bands in the 3500-3000 cm^{-1} region corresponding to NH groups involved in diverse types of inter and intra-molecular hydrogen bonds; the position of these lines differs strongly in various compounds. In view of the insignificant solubility of the reaction products, it was impossible to record spectra in dilute solution.

UV spectral data were used for clarification of the structure of the tetrahydroimidazole derivatives obtained. Long-wavelength maxima were found in the 330 nm region. With previously synthesized alkyl amides of aroylpyruvic acids in which there was interaction between the aroyl and alkylcarbamide moieties as a result of complete enolization of these compounds, the long-wavelength maximum also was observed in the 336 nm region [5].

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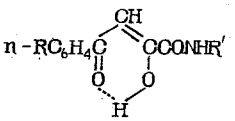
TABLE 1. 5-Phenacylidenyltetrahydroimidazole-2,4-diones (II)

R	Preparative method	Yield, %	mp, °C	Found, %			Empirical formula	Calc., %		
				C	H	N		C	H	N
H (IIa)	A	89	207—8	58,67	3,81	12,92	$C_{10}H_8N_2O_3$	58,82	3,92	12,91
	B	97								
CH_3	A	90	245—6	60,35	4,48	12,09	$C_{11}H_{10}N_2O_3$	60,55	4,58	12,17
	B	99								
CH_3O	A	96	213—4	56,30	4,15	11,20	$C_{11}H_{10}N_2O_4$	56,41	4,27	11,38
Cl (IIb)	A	90	263—4	50,01	2,72	11,00	$C_{10}H_7ClN_2O_3$	50,31	2,93	11,17
	B	98								
Br (IIc)	A	68	274—5	42,30	2,25	9,67	$C_{10}H_7BrN_2O_3$	42,40	2,47	9,49
	B	86								
F	A	94	274—5	53,83	3,00	12,16	$C_{10}H_7FN_2O_3$	54,05	3,15	11,96
$(CH_3)_3$	A	78	200	63,29	5,60	10,98	$C_{13}H_{14}N_2O_3$	63,41	5,69	10,85

TABLE 2. Pharmacological Properties of Compounds IIa-c

Compound	Anticonvulsive activity, ED_{50}, mg/kg				Acute toxicity, LD_{50}, mg/kg	Side effects, TD_{50}, mg/kg, by rotating rod test	Therapeutic index, LD_{50}/ED_{50}	Protection index, TD_{50}/ED_{50}
	peak activity, h	internal introduction	peak activity, h	peritoneal introduction				
IIa	1	335 (274—408)	1	170 (154—187)	780 (675—900)	400 (352—454)	4,6	2,4
IIb	1/2	400 (316—504)	1/2	290 (244—344)	1200 (1000—1400)	420 (348—506)	4,1	1,4
IIc	1	315 (264—374)	1	240 (190—302)	1470 (1195—1808)	360 (299—434)	6,1	1,5
Diphenylhydantoin	—	—	1/2	45 (40—50)	890 (712—1113)	78 (68—89)	19,8	1,8



In addition, for the arylamide of β-bromopyruvic acid, corresponding to the keto form in which the aroyl and arylamide moieties are separated, there was a long-wavelength maximum at 226 nm [5].

Thus the position of the long-wavelength maximum for these derivatives of tetrahydroimidazoles corresponds largely to form II, in which there is an interaction between the aroyl system and the imidazole ring. This finding is confirmed by the similar absorption curves for the morpholide of α-morpholinobenzoylacrylic acid and for 5-benzalidinotetrahydroimidazole-2,4-dione which conform very closely in the form and arrangement of their long-wavelength maxima (332 nm).

The presence of interaction between the aroyl fragment and the imidazole nucleus also is confirmed by the influence of the para-substituent of the aroyl group on the position of the long-wavelength maxima.

EXPERIMENTAL RESULTS

Pharmacology

The ACA and toxicity of 5-phenacylidenyltetrahydroimidazole-2,4-dione (IIa), 5-(p-chlorophenacylidenyl)-tetrahydroimidazole-2,4-dione (IIb), and 5-(p-bromophenacylidenyltetrahydroimidazole-2,4-dione (IIc) were studied by comparison with diphenylhydantoin on 1200 white mice, equally distributed as to sex.

The ACA was measured by the maximal electroshock (MES) test as modified by K. S. Raevskii [6] and the Corazole (benzylenetetrazole) test [7]. The results of the tests were treated statistically [8] to calculate the value of ED_{50}. Acute toxicity was determined according to G. N. Pershin [9], and side effects by the "rotating rod" test [10] to give statistically calculated LD_{50} and TD_{50} at $P = 0.05$ by the same method. We also studied the influence of the compounds at a dose equal to one-fifth of the LD_{50} on the duration of Hexenal (Hexobarbital) narcosis, Medinal (Sodium Barbital) sleep, and on the convulsive activity of Bemegrid. Hexenal (70 mg/kg), Medinal (200 mg/kg), and Bemegrid (20 mg/kg) were administered intraperitoneally 1 h after the introduction IIa and IIb and 30 min after the introduction of IIc, which accordingly induced control of narcosis over a period of 28.0 ± 11.4 min, of sleep over a period of 137.0 ± 33.4 min, and of convulsions of half of the animals taken in the experiment. These results were treated statistically [11]. We calculated the therapeutic index (ratio of LD_{50} to ED_{50} for MES), and also the protection index (ratio of TD_{50} for the "rotating rod" test to ED_{50} for MES). Because of their insolubility in water, the test compounds and diphenylhydantoin were introduced intraperitoneally and internally in the form of suspensions in 2% starch paste.

Table 2 shows that IIa-c possess ACA by both methods of introduction. By intraperitoneal introduction, the ACA of IIa-c is lower than diphenylhydantoin by 3.7 (3.2-4.2), 6.4 (4.2-9.6) and 5.3 (4.1-6.8) times, respectively; the difference for the ACA of IIb and IIc is statistically insignificant, but IIa is more active than IIb and IIc by 1.7 (1.5-1.9) and 1.4 (1.1-1.8) times. For internal introduction, the ACA differences of IIa-c were statistically insignificant, the ACA of IIc being the same for both methods of introduction. Compounds IIa and IIb were more active by intraperitoneal introduction than by internal introduction by 2.0 (1.6-2.5) and 1.4 (1.1-1.9), respectively. Compounds IIa-c did not possess ACA by the Corazole test. The difference in acute toxicity of IIa and IIb by comparison with diphenylhydantion is not statistically significant, but IIc is 1.6 (1.2-2.1) times less toxic. Side effects by the "rotating rod" test on IIa-c were less than with diphenylhydantoin by 5.1-5.5 times, and the therapeutic index was lower by 3.8-4.8 times. The protection indices for IIb and IIc were somewhat lower, but were higher for IIa. Compounds IIa-c extended Hexenal narcosis by 36.7 ± 14.6, 50.2 ± 20.8, and 51.2 ± 25.1 min, respectively, i.e., by 1.3 and 1.7 times. Compound IIa did not influence the length of Medinal sleep (the decrease did not reach statistical significance) but compounds IIb and IIc lengthened it by up to 2 days. Compounds IIb and IIc amplified convulsions induced by Bemegrid by 25-30%, and IIb was essentially without effect on the course of the convulsions.

The compounds presumably depress the activity of the microsomal enzymes of the liver by incremental steps (IIa < IIb < IIc) and show a depressant action on the central nervous system. The results of the study show that among the derivatives of 5-phenacylidenyltetrahydroimidazolediones can be found preparations which possess ACA and having less side effects than diphenylhydantoin.

IR spectra were obtained with a UR-20 instrument in mineral oil mulls. UV spectra were taken with a "Specord UVvis" spectrometer at a sample concentration of 10^{-4}M in ethanol.

5-Phenacylidenyl-1,3-imidazole-2,4-dione (II). Method A. A mixture of equivalent quantities of benzoylpyruvic acid and urea was mixed at 130°C for 1 h in a paraffin oil bath with subsequent recrystallization of the product from acetic acid (1:1).

Method B. A mixture of equivalent quantities of 5-arylfuran-2,3-dione and urea was stirred in a paraffin oil bath at 100-110°C for 20 min.

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AZACYCLOALKANES

XXII. SYNTHESIS AND ANTIANGINAL PROPERTIES OF NONACHLAZINE AND NONAPHTAZINE

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One of the pressing problems of modern pharmacology is the search for antianginal agents with a new type of action that can influence the main regulatory processes responsible for blood supply, metabolism, and cardiac function.

It has already been shown in the preceding communication that many of the diazabicycloalkyl derivatives of N-acylphenothiazines can improve the blood supply to the heart. Two of them, 10-[β-N-(1,4-diazabicyclo-[4,3,0]nonanyl)propionyl]-2-trifluoromethylphenothiazine (IVa) and 10-[β-N-(1,3-diazabicyclo[4,3,0]nonanyl)-propionyl]-2-chlorophenothiazine (IVb) dihydrochlorides, named respectively nonaphtazine and nonachlazine, were found to be especially promising; the present paper describes their synthesis and pharmacological study.

These compounds were obtained according to the reaction scheme on the following page.

1,4-Diazabicyclo[4,3,0]nonan-5-one (I) was reduced by lithium aluminum hydride in dry triethylamine (cf. [1]) to 1,4-diazabicyclo[4,3,0]nonane (II). The reaction of the amine II with 2-substituted β-chloropropionyl-phenothiazines (IIIa, b) in toluene with an equimolecular ratio of the reagents and with triethylamine as the

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