REACTIONS OF ALIPHATIC DIAZO COMPOUNDS XX. SYNTHESIS AND INVESTIGATION OF THE ANTISPASMODIC ACTIVITY OF ARYL-SUBSTITUTED α-DIAZOKETONES

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We carried out the synthesis of a series of substituted diazoketones and investigated their antispasmodic activity. The synthesis of the preparations was carried out by the method of Arndt and Eistert.

$$RCOCl+2CH_2N_2\rightarrow RCOCHN_2+CH_3Cl+N_2$$

The investigation of aryl-substituted diazoacetones was of special interest because it is known that the amides of aryl-substituted acetic acids possess a rather high antispasmodic activity [1]. Both the already known aryl-substituted diazoketones (I–IV, VII, IX, Table 1) [2–6] and compounds which have not been described in the literature were synthesized for the investigation.

Our attempts to replace the chlorine in chloradiazoacetone by nitrate, nitrile, carbonyl, succinimide, and other groups by reacting the diazoketone with the appropriate silver compounds failed. This is evidently explained by the decrease in the electrophilicity of the carbon bonded to the chlorine through a shift in the electron cloud, which envelops the conjugated $COCHN_2$ system, toward the oxygen of the carbonyl group [7]. The introduction of a phenyl group into the chlorodiazoacetone molecule does not increase the mobility of the chlorine atom, and we also did not succeed in inducing phenylchlorodiazoacetone to react with the silver compounds mentioned above. The chlorine atom in diphenylchlorodiazoacetone becomes sufficiently mobile and is easily substituted by a nitrate group by the action of silver nitrate in an acetonitrile medium.

$$(C_6H_5)_2\underset{\underset{Cl}{|}}{C}COCHN_2 + AgONO_2\rightarrow (C_6H_5)_2\underset{\underset{ONO_2}{|}}{C}COCHN_2 + AgCl$$

VIII

The compound obtained (VIII) is the first example in the series of nitroxy-substituted α-diazoketones.

The absorption bands in the 2125–2115 cm^{-1} region due to the diazo group and in the 1660–1625 cm^{-1} region due to the conjugated carbonyl group are easily identified in the IR spectra (see Table 1) of the diazoketones. It is interesting that the introduction of a nitrate group into the diazoketone molecule leads to a shift in the carbonyl absorption band toward higher frequencies. This indicates that there is a decrease in the degree of p–π–p conjugation in the $COCHN_2$ fragment through the electron acceptor properties of the nitrate group. A weakening of the conjugation in the diazocarbonyl fragment also takes place under the influence of the phenyl substituents; this is especially highly noticeable in the series phenyl-, diphenyl-, and triphenyldiazoacetones. A still greater effect is observed for α-diazoacetophenone because the aromatic ring in this case is an electron donor.

The antispasmodic activity of the α-diazoketones we synthesized was investigated on mice using the maximum electroshock (seizure) test [8] and Corazol test [1, 9, 10].

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TABLE 1. Substituted α-Diazoketones $PCOCHN_2$

Compound	R	Yield (in %)	Melting point (in deg)**	IR spectrum (in cm^{-1})	
				νN≡N	νC=O
I	$C_6H_5CH_2$	88	42--3	2120	1630
II	C_6H_5	85	43—5	2108	1620
III	$(C_6H_5)_2CH$	46	58—60	2120	1635
IV	$(C_6H_5)_3C$	57	151--2	2120	1650
V	$(C_6H_5)_2CCl$	45	45—7	2125	1625
VI	C_6H_5CHCl	27	54—6	2120	1645
VII*	C_6H_5	66	63—4	2100	1660
VIII	$(C_6H_5)_2CONO_2$	36	82—3	2120	1660
IX		93	69—70	2115	1630

*The α-hydrogen atom in compound VII is substituted by an acetyl group.

**Compound I was crystallized from petroleum ether; II and VIII from hexane; III, V, and VII from ethanol; IV from toluene; VI from decane; and IX from methanol.

TABLE 2. Antispasmodic Activity of α-Diazoketones

Compound	AU_{50} (in mg/kg)* according to the maximum electroshock (seizure) test
I	107,0 (93,8—121,9)
II	not active
III	225,0 (174,5—297,0)
IV	not active
V	not active
VI	350,0 (296,0—113,0)
VII	195,0 (175,0—216,4)
VIII	220,0 (177,4—272,8)
IX	740,0 (578,0—947,0)
Phenobarbital	15,5 (12,8--18,8)

*The confidence limits of the AU_{50} were calculated for $p = 0.05$.

Spasms according to the maximum electroshock (seizure) test were brought about in the following way: silver electrodes were applied to the mouse's eye, an alternating electric current of 50 mA was passed through them for 0.2 sec with a vibrational frequency of 50 cycle/sec. This "dose" of electric current caused clonic-tonic spasms in all the mice. The antispasmodic action was judged by the (degree of) removal of the extensor phase of the spasmodic attack within $^1/_2$, 1, 2, 3, and 4 h after the injection of the preparations. The results were treated statistically by the method of Litchfield and Wilcoxon [11] while determining the AU_{50}. The fullest development of the antispasmodic activity of a preparation was judged from the lowest AU_{50} value (obtained) after its injection. The length of time it was active was taken as the peak of the antispasmodic action of the AU_{50} (dose) as determined by the maximum electroshock (seizure) test, and all further investigations in determining the antispasmodic and antitremor activity by other tests were carried out with this dose and at the peak of the activity.

The Corazol spasms were brought about by the intraperitoneal injection of 70 mg/kg of Corazol as a 0.7% aqueous solution in volumes of 0.1 ml for each 10 g of weight of the mouse. Spasms with a strength of three points develop in all the mice from this dose of Corazol; half of them die. The strength of the spasms are evaluated visually according to a three-point system: one point (is given) for clonic spasms with the mouse being in its natural posture; two points (are given) for clonic-tonic spasms with a forced convulsive movement of the mice and with the presence of positions unnatural for them during the spasms (on their side, on their back, etc.); three points (are given) for substantial clonic-tonic and topic spasms when the mice are thrown upward during the spasmodic attacks, and when they fall, they do not maintain a posture that is natural for them; and the spasms also continue after they fall [10].

The antispasmodic activity of the preparations according to the Corazol test was judged from their ability, using an AU_{50} dose as determined from the maximum electroshock (seizure) test, to prevent or decrease Corazol spasms by one or two points in all the mice used in the experiment.

The antitremor activity of the α-diazoketones was determined by their ability, in AU_{50} doses as determined by the maximum electroshock seizure test, to prevent the onset of tremor in the mice from nicotine at a dose of 8 mg/kg or arecoline at a dose of 30 mg/kg both of which were injected intraperitoneally as an aqueous solution in volumes of 0.1 ml for every 10 g of weight of the mouse.

The antispasmodic activity of the α-diazoketones was compared to that for phenobarbital.

The α-diazoketones were injected intraperitoneally as a 2% starch mucliage, becuase of their insolubility in water, in increasing doses up to 600 mg/kg. When there was no activity at a dose of 600 mg/kg, even if in only one animal of the group, the preparation was considered to be not active.

Their stimulating and depressing effects, on the central nervous system were determined visually.

Six of the nine α-diazoketones investigated possess antispasmodic activity according to the maximum electrochock seizure test (Table 2). Thus, α-diazoketones are a new class of preparations which manifest antispasmodic activity.

The peak of their antispasmodic effect for an AU_{50} dose, as determined by the maximum electroshock seizure test, is manifested within 2 h by diazoketone VIII and within 1 h by all the others. The α-diazoketones are ranked as follows according to the strength of their antispasmodic activity: I > VII > VIII > III > VI > IX. All the diazoketones are 7-23 times less active than phenobarbital.

Compounds VI and VIII in AU_{50} doses, as determined by the maximum electroshock sezure test, also decrease Corazol spasms up to one point.

Thus, the introduction of a chlorine and nitrate group into phenyl-substituted α-diazoketones broadens the spectrum of their antispasmodic activity (compare I, III with VI, VIII). The introduction of a chlorine (group) into phenyldiazoacetone (I) leads to a greater than three-fold decrease (VI) in antispasmodic activity, and the introduction of a chlorine (group) into diphenyldiazoacetone (III) leads to the loss of antispasmodic activity by the preparation (V). The antispasmodic activity also decreases when phenyl groups are introduced into compound I. Preparation III is less active than I, and triphenyldiazoacetone (IV) possesses no antispasmodic activity. The aryl-substituted diazoketones also lose their antispasmodic activity when the phenyl group is directly bonded to the carbonyl group (II), but the activity is restored when the α-hydrogen atom is substituted in diazoketone II by an acetyl group (VII).

Preparations I, III, VI, and VIII in AU_{50} doses, as determined by the maximum electroshock seizure test, exert no antitremor activity according to the nicotine and arecoline tests when injected intraperitoneally into mice, i.e. they do not manifest H- and M-cholinolytic activity.

Compounds I, III, and VIII bring about a short-lived tranquilizing effect; VI effects stimulating activity in doses of more than 350 mg/kg, and VII causes a disruption of motor coordination in doses greater than 200 mg/kg.

Compounds I, III, and VI-IX did not kill any mice within one day when injected intraperitoneally in doses up to 600 mg/kg.

EXPERIMENTAL

Aryl-Substituted α-Diazoketones (I-VI). An ether solution of 0.1 mole of the acid chloride was slowly added with vigorous agitation at 0 to −5°C to an ether solution of 0.3 mole of diazomethane. The reaction mixture was maintained for 1-2 h at room temperature, and the ether was distilled off along with the excess diazomethane. The remainder was recrystallized. Diazoketones I, II, III, IV, VII, and IX were identified by comparing them with previously known samples [2-6]. For V the following was found, %: C 66.54; H 4.12, N 9.89. $C_{15}H_{11}ClN_2O$. Calculated, %: C 66.50; H 4.07; N 10.37. For VI the following was found, %: C 55.42; H 3.60; N 14.31. $C_9H_7ClN_2O$. Calculated, %: C 55.67; H 3.61; N 14.43.

3-Nitroxy-3,3-diphenyl-1-diazoacetone (VIII). To 1 g of diazoketone V dissolved in 20 ml of acetonitrile was added with agitation a solution of 0.7 g of silver nitrate in 10 ml of acetonitrile. The reaction mixture was maintained for 30 min at room temperature, and the silver chloride precipitate was filtered off. The filtrate was evaporated to dryness in vacuo and the residue was recrystallized, m.p. 82-83°C (from hexane). Found, %: C 61.01; H 3.91; N 14.01. $C_{15}H_{11}N_3O_4$. Calculated, %: C 61.60; H 3.73; N 14.14. The frequencies of the following groups were detected in the IR spectrum: ν N ≡ N 2120, ν CO 1660, and ν ONO_2 1290 cm^{-1}.

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