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MELDRUM'S ACID AND ITS ANALOGS

A. N. Kost, L. N. Khaimov,
Yu. Dzhurakulov, K. Kh. Khaidarov,
L. D. Lebedeva, and A. L. Kotov

UDC 547.841:543.422.25'51

2-Substituted or 2,2-disubstituted 4,6-dioxo-1,3-dioxanes, which are analogs of Meldrum's acid and were obtained by reaction of malonic acid with acetic anhydride and the appropriate carbonyl compound in the presence of sulfuric acid, exist in solution preferably in a single form according to the PMR and ^{13}C NMR spectral data. Fluctuation of the CH_2 group is not observed. The mass spectra are characteristic and are distinguished by splitting out of the carbonyl compound from the molecular ion or successive splitting out of CO_2 and ketene molecules. The Meldrum acid analogs do not affect plant growth but have a depressive effect on the central nervous system of animals and low toxicity.

The structure and reactivity of Meldrum's acid, i.e., 2,2-dimethyl-4,6-dioxo-1,3-dioxane (Ia), to which the 3,3-dimethyl-2-carboxy-β-propiolacetone structure had been assigned for a long time in view of its considerable acidity and the practical absence of enolization [1-3], up until now have given rise to misunderstandings, especially since the arylidene derivatives of Meldrum's acid and its analogs behave like neutral Lewis acids in that they readily add hydroxide ions [4]. The problem of the conformation of such structures is also in debate. Moreover, despite the accessibility of such models and their formal similarity to barbituric acid derivatives, the literature contains no information regarding the biological effect of Meldrum's acid and its analogs.

We have synthesized Meldrum's acid and some of its analogs (Ia-g) using the reaction of malonic acid with the appropriate carbonyl compound in the presence of acetic anhydride [1, 2, 5]. The yields are satisfactory when ketones of the aliphatic, alicyclic, or aliphatic-aromatic series are used in the reaction. Pronounced resinification was observed in the case of aliphatic aldehydes having an α-hydrogen atom, and we were unable to obtained the desired compound from cuminaldehyde.

The IR spectra of the synthesized compounds contain two intense absorption bands of ester carbonyl groups at 1740-1770 and 1780-1800 cm^{-1}. The UV spectra have pronounced absorption with maxima at

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M. V. Lomonosov Moscow State University. Tadzhik Agricultural Institute. Institute of Chemistry, Academy of Sciences of the Tadzhik SSR, Dushanbe. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1482-1486, November, 1975. Original article submitted December 19, 1974.

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TABLE 1. Meldrum's Acid and its Analogs

Compound	R	R'	mp, °C	R_f	Electrophoretic mobility, U, 10^5 cm²/sec	Yield, %
Ia	CH_3	CH_3	96—97[14]	0,35	1,7	55
Ib	C_6H_5	H	145—146[15]	0,38	1,6	48
Ic	$(CH_2)_5$		84—85[14]	0,50	1,2	31
Id	C_2H_5	$C_6H_5CH_2$	98—99*	0,61	0,6	44
Ie	C_6H_5	CH_3	91—92[16]	0,60	2,1	23
If	p-ClC_6H_4	H	154—155[16]	0,45	—	16
Ig	p-$NO_2C_6H_4$	H	123—124†	0,50	2,3	32
	Compound II		82—83[17]	0,46	5,4	48

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*Found: C 66.4; H 5.3%, $C_{13}H_{14}O_4$. Calculated: C 66.6; H 5.6%.

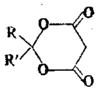
†Found: C 50.4; H 2.7%. $C_{10}H_7NO_6$. Calculated: C 50.6; H 2.9%.

250-260 nm and weak absorption of 320-330 nm. In alkaline media the shortwave maximum is shifted reversibly to 270-275 nm with a considerable increase in extinction, and this corresponds to the appearance of conjugation of two carbalkoxy groups through the carbanion. The introduction of a phenyl residue in the molecule gives rise to the appearance of additional absorption at ~250 nm. These results correspond to the information available on the UV and IR spectra of acids of the I type [6-8]. All of the compounds obtained in this study are weak CH acids, like Meldrum's acid itself [2, 8], with close ionophoretic mobilities (see Table 1). They react with amines to give salts.

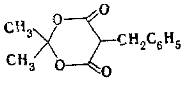
Having in view a study of the biological activity of such structures, we first of all turned to an evaluation of their conformations. Two opinions have been recently expressed on the basis of studies of their dipole moments. According to one of these opinions, acid Ia in solution exists in the form of a mixture of chairlike and boatlike forms with predominance of the latter [9]; according to the other opinion [1)], this substance has a compressed half-chair conformation. However, calculations made by one or the other group of authors gave dipole moments that differ substantially from the experimentally found values. At the same time, there are PMR spectral data [11] that constitute evidence in favor of the existence of Ia in the form of a mobile equilibrium of two easily convertible forms, whereas its unsymmetrically constructed alalogs (Ib and II) exist in a single most-stable conformation.

We obtained a clear spectrum of acid Ia in trifluoroacetic acid and a lower-quality spectrum (in view of the low solubility of the substance) in CCl_4. Both spectra have a 6 H singlet (2 methyl groups) and a singlet of protons of the CH_2 group. The ^{13}C spectrum of this same compound in chloroform has distinct signals of the carbon atoms of a carbonyl group (163.3 ppm), of a quaternary (i.e., acetal) carbon atom (106.2 ppm), of a methylene group (36.0 ppm), and two methyl groups of the same type (27.4 ppm). The assignment of these signals was confirmed by PMR. Thus our data confirm the existence of Meldrum's acid in solution in the form of an equilibrium mixture of rapidly convertible conformers.

When the methyl groups in acid are replaced by a spirocyclohexane system (Ic), the symmetrical character of the model is retained, and this, in conformity with the concepts of Pihlata and Sello [12], should have preserved the capacity of the methylene group for fluctuation. However, two singlet protons of a CH_2 group with chemical shifts of 3.68 and 3.88 ppm are distinctly seen in the PMR spectra of Ic in trifluoroacetic acid (in addition, at strong field there are two broadened triplets centered at 2.50 and 3.0 ppm and a multiplet of six protons at 1.3-2.2 ppm). Consequently, Ic exists in solution preferable in one conformation, probably in a chairlike conformation (for both rings). The introduction of a benzyl substituent in the methylene group, in conformity with the observations of Pihlata and Sello [12], gave the highly



Ia-g



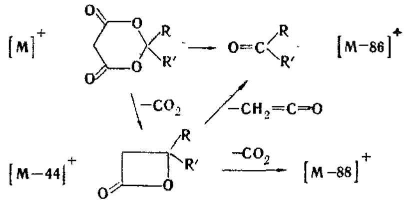
II

I a $R=R'=CH_3$; b $R=H$, $R'=C_6H_5$; c $R+R'=(CH_2)_5$; d $R=C_2H_5$, $R'=C_6H_5CH_2$; e $R=$ $=CH_3$, $R'=C_6H_5$; f $R=H$, $R'=p$-ClC_6H_4; g $R=H$, $R'=p$-$NO_2C_6H_4$

CCl_4-soluble II, the PMR spectrum of which has a singlet of phenyl protons at 7.72 ppm, a multiplet of a $CHCH_2$ group at 3.78-4.28 ppm with J=4 Hz, and two singlets of methyl groups at 1.75 and 2.03 ppm (at 1.51 and 2.06 ppm in chloroform).

The PMR spectral data for II are confirmed by the ^{13}C spectrum (in chloroform), in which signals of a carbonyl group (165.3 ppm), of aromatic ring carbon atoms (127.1, 128.3, 129.5, and 137.2 ppm), of an acetal carbon atom (105.1 ppm), of $CHCH_2$ groups (48.0 and 32.1) and each of the CH_3 groups (28.3 and 27.0 ppm) are observed. The absence of a second signal of the CH group and the presence of two independent signals of the methyl groups confirm the existence of the substance in one stable conformation.

The mass spectra of Id, c, e have a system of peaks that attest to competitive processes of fragmentation of the molecular ion of such structures, namely, with splitting out of a fragment of the carbonyl compound (retrocyclization with the formation of the $[M-86]^+$ ion), or successive splitting out of a CO_2 molecule and ketene. Compound Ib, for which the molecular ion peak is a maximum, is the most resistant to electron impact. In the case of Ie, elimination of the methyl group in the gem position procedes splitting out of CO_2 and ketene.



It is known that plant growth stimulators are usually carboxylic acids or have some other weak acidic group [13]. The compounds that we synthesized practically did not stimulate the rooting of bean scions in a concentration of $5 \cdot 10^{-4}$ mole/liter, and concentrations of $5 \cdot 10^{-6}$ mole/liter even suppressed somewhat the development of the root system. Similarly, in experiments on wheat coleopters, most of the investigated substances somewhat suppressed plant growth at concentrations from $1 \cdot 10^{-3}$ to $1 \cdot 10^{-5}$. Pronounced growth stimulating activity was observed in the case of Ib, but this activity was substantially lower than that of known preparations – indolylacetic and indolylbutyric acids. Experiments with radish seeds showed that activity was practically absent or, in the case of high concentrations, that growth was somewhat suppressed. Similar results were obtained in a study of the action of our substances on the growth of cucumber roots. Thus Meldrum's acid and its analogs have only a slight stimulating effect on plants, and high concentrations of them somewhat suppress their growth.

Depression was observed when white mice were injected intraperitoneally with 100-950 mg/kg doses of I and II, while sublethal doses produced a soporific effect. The toxicity of the preparations is low – LD_{50} 560-860 mg/kg. The preparations do not affect diuresis. Meldrum's acid Ia potentiates hexenal-induced sleep beginning with doses of 300 mg/kg (LD_{50} 560 mg/kg); it does not have pronounced antispasmodic activity. Prior injection of this preparation in doses of 400-500 mg/kg prolonged the time during which Corozole-induced spasms are manifested without changing their character. The other investigated substances also have a similar effect, although in the case of II (LD_{50} 680 mg/kg) an antispasmodic effect is not expressed even with 400 mg/kg doses vis-a-vis considerable potentiation of hexenal-induced sleep, while Id (LD_{50} 860 mg/kg) displayed primarily antispasmodic activity (in doses of 400 to 500 mg/kg). A sedative effect without a soporific effect was observed in the case of Ic. This preparation clearly prevents Corazole-induced spasms in doses of 400-500 mg/kg, although it does not completely eliminate the toxic effect of Corazole. None of the preparations affected the cardiovascular system or isolated intestines.

Thus Meldrum's acid and its analogs have only slight toxicity and a pronounced depressive effect on the central nervous system (CNS), and this is of promise for the future search for medicinals in this direction.

EXPERIMENTAL

The UV spectra of ethanol solutions of the compounds were obtained with Cary-15 and Specord spectrophotometers. The IR spectra of mineral oil suspensions of the compounds were recorded with an IKS-22 spectrometer. The PMR spectra were obtained with Varian T-60 or PC-60 spectrometers with hexamethyldisiloxane as the external standard. The ^{13}C NMR spectrum was kindly recorded by V. B. Leont'ev (Tashkent University) with a Varian 620/f spectrometer. The width of the spectrum was 5000 Hz, and the time lag after recording of a pulse was 1 sec. The individuality of the substances was monitored by chromatography on Silufol UV-254 plates with elution with methanol–benzene (1 : 9). The mass spectra were obtained with an MKh-1303 spectrometer with introduction into the ion source; the temperature was 80°, the ionizing voltage was 50 eV, and the current strength was 150 mA. Ionophoresis was carried out with "Leningrad medium" paper in aqueous solution with a pyridine–acetate buffer (pH 5.2) with an electrophoretic chamber of the horizontal type and a PÉF-1 stabilizer; the voltage was 350 V, the chromatograms were developed by UV irradiation or with iodine vapors, and the recording time was 3 to 6 h.

2,3-Dimethyl-4,6-dihydroxy-1,3-dioxane (Meldrum's acid, Ia). Three to four drops of concentrated H_2SO_4 were added to a solution of 10.4 g (0.1 mole) of malonic acid in 40 g of acetic anhydride, after which the mixture was shaken until it was completely homogeneous (during which it spontaneously underwent pronounced cooling). It was then allowed to stand overnight. The excess acetic anhydride was removed by vacuum distillation (3-5 mm) at a water bath temperature of 40-50° and freshly distilled acetone [11.6 g (0.2 mole)] was added to the syrupy residue, during which the mixture spontaneously warmed up slightly and turned brown. The resulting precipitate was separated, air dried, and recrystallized from alcohol to give 6.6 g (55%) of a substance with mp 96-97°. IR spectrum, ν, cm^{-1}: 1760 and 1800. UV spectrum λ ($\log \varepsilon$): 256 (2.20) and 332 (1.76) nm. PMR spectrum in CF_3COOH: singlets at 1.72 ($2CH_3$) and 3.84 (CH_2) ppm; in $C_6H_5NO_2$ 1.45 ($2CH_3$) and 3.52 (CH_2) ppm (in agreement with the literature data [1, 14]. Found: C 50.0; H 5.8%. $C_6H_8O_4$. Calculated: C 50.0; H 5.6%.

Compounds Ib-h and II (from benzylmalonic acid) were similarly obtained (see Table 1). The results of elementary analysis of these substances corresponded satisfactorily to the calculated values.

Piperidine Salts. These salts were obtained by the method described in [18]. Compound Ia gave a salt with mp 117-118° (from alcohol) in 95% yield. Found: C 57.1; H 8.4; N 5.9%. $C_{11}H_{19}O_4$. Calculated C 57.6; H 8.3; N 6.1%. The salt of acid Ic had mp 114-115°. Found: C 62.5; H 8.6; N 5.1%. $C_{14}H_{25}NO_4$. Calculated: C 62.8; H 9.5; N 5.2%. The salt of acid Id had mp 116-117 (dec.). Found: C 68.5; H 7.9%. $C_{18}H_{25}NO_4$. Calculated: C 68.7; H 7.8%.

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