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SYNTHESIS OF γ -BUTYROLACTONES FROM AMIDO DERIVATIVES OF AROMATIC KETONES

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Derivatives of γ -butyrolactones were synthesized by bromination of N,N^1 -disubstituted (1-phenyl-2-benzoyl)ethylmalonic acid amides.

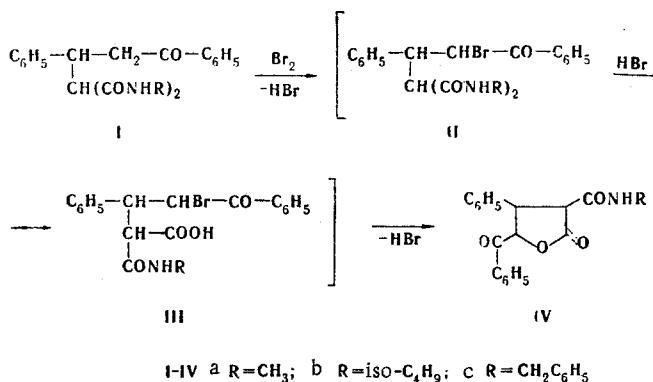
It is known that spiroketolactones [1, 2] are formed by bromination of amido derivatives of indanediones and tetalones. In the present research we have studied the possibility of the preparation of γ -butyrolactones from amido derivatives of noncyclic aromatic ketones. Inasmuch as the γ -butyrolactone ring is present in a number of natural antibiotics and alkaloids [3, 4], its formation seems of interest for the synthesis of potential physiologically active compounds.

(1-Phenyl-2-benzoyl)ethylmalonic acid N,N^1 -dialkylamides (Ia-c) [5] were used as the starting compounds. α -(N-Alkylcarbamoyl)- β -phenyl- γ -benzoyl- γ -butyrolactones IVa-c were isolated in the bromination of diamides Ia-c with bromine in acetic acid.

Like the IR spectra of starting amides I, the spectra of lactones IV contain the absorption of a ketone carbonyl group at $1685-1699\text{ cm}^{-1}$ and of an amide carbonyl group at $1665-1670\text{ cm}^{-1}$. In contrast to the spectra of starting amides I, an intense maximum at $1778-1790\text{ cm}^{-1}$,

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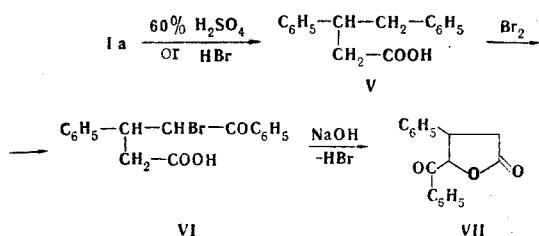
I-IV a R=CH₃; b R=iso-C₄H₉; c R=CH₂C₆H₅

which is characteristic for the carbonyl group of a five-membered lactone, appears in the spectra of lactones IV. The spectra of lactones IV also contain NH absorption at 3300-3380 cm⁻¹.

Doublets of ring methylidyne protons (J = 6.0 Hz) are observed in the PMR spectra (in CDCl₃) of lactones IVa-c. The signal of a methylidyne proton attached to C-3 appears at 3.60-3.67, the signal of a methylidyne proton attached to C-4 appears at 5.78-6.05, and the signal of a methylidyne proton attached to C-2 appears at 4.40-4.42 ppm. The NH signal is broadened and is observed at 6.70-6.90 ppm. In the spectrum of IVa, the nitrogen atom of which is bonded directly to a methyl group, the signal of the corresponding protons (2.80 ppm) is a doublet (J = 5.9 Hz). The existence of spin-spin coupling between the CH₃ and NH protons was proven by double resonance (exposure of the NH signal at 7.36 Hz to an additional field converts the NCH₃ doublet to a singlet).

We assume that the course of the reaction is similar to that described in [1, 2]. Bromo derivative II is formed, and the liberated hydrogen bromide promotes saponification of one amide group to a carboxyl group to give γ -bromo acid III, which readily splits out a molecule of HBr to give a lactone ring.

A second method for the preparation of γ -butyrolactone VII was proposed, consisting in saponification of diamide Ia and subsequent bromination and cyclization. During saponification, both amide groups are hydrolyzed, one of which undergoes decarboxylation to give acid V. Bromination of acid V with an equivalent amount of bromine gives β -phenyl- γ -bromo- γ -benzoylbutyric acid VI, which on treatment with a weak alcohol solution of alkali is cyclized to β -phenyl- γ -benzoyl- γ -butyrolactone VII.



Carbonyl absorption of a ketone at 1680 and of an acid at 1710 cm⁻¹ is observed in the IR spectrum of acid V. A broad band of stretching vibrations of the associated bond of the hydroxyl group of an acid is present at 2600-3200 cm⁻¹.

In addition to signals from the protons of the phenyl group, the PMR spectrum of acid V (in CF₃COOH) contains signals of methylene and methylidyne protons in the form of multiplets centered at 2.98 and 3.55 ppm, respectively. In the PMR spectrum of brominated acid VI (in CF₃COOH) the signal of the methylidyne proton attached to the same carbon atom as the bromine atom is shifted to weak field to 5.58 ppm.

Just as in the spectra of acids V and VI, the IR spectrum of lactone VII contains CO absorption at 1680 cm⁻¹. In addition, an intense CO band of a five-membered lactone appears in the spectrum of lactone VII at 1778 cm⁻¹.

TABLE 1. Physical Characteristics of the Synthesized IV-VIII

Compound	mp, °C	Empirical formula	Found, %			Calc., %			IR spectra, cm ⁻¹ (% absorption)				Yield, %
			C	H	N	C	H	N	ν_{CO}	ketone ν_{CO}	lactone ν_{CO}	ν_{NH}	
IVa	168—169	C ₁₉ H ₁₇ NO ₄	70.5	5.3	4.2	70.6	5.3	4.3	1665 (75)	1697(74)	1778(84) (72)	3300	62
IVb	147—148	C ₂₂ H ₂₃ NO ₄	72.5	6.4	4.0	72.3	6.3	3.8	1655 (82)	1690(78)	1790(86) (83)	3305	57
IVc	170—171	C ₂₅ H ₂₁ NO ₄	75.3	5.4	3.4	75.2	5.3	3.5	1670 (90)	1685(88)	1785(83) (90)	3380	35
V	156—158	C ₁₇ H ₁₆ O ₃	76.5	6.1	—	76.1	6.0	—	—	1680(76)	ν_{CO} (acid)	—	63
VI	178—179	C ₁₇ H ₁₅ O ₃ Br*	58.9	4.4	—	58.8	4.4	—	—	1675(70)	1710(82)	—	52
VII	128—129	C ₁₇ H ₁₄ O ₃	76.8	5.4	—	76.7	5.3	—	—	1680(58)	1712(84) 1778(76)	—	52

*Found: Br 23.7%. Calculated: Br 23.0%.

The PMR spectrum of lactone VII is similar to the spectra of lactones IV, but, in contrast to the spectra of IV, a signal of methylene protons attached to C-2 appears at 3.05 ppm.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil and hexachlorobutadiene were recorded with a UR-20 spectrometer. The PMR spectra of solutions in CDCl₃ and CF₃COOH were recorded with a Perkin-Elmer R-12A spectrometer (60 MHz) with tetramethylsilane as the internal standard.

The physical characteristics of the compounds and the IR spectral data are presented in Table 1.

α -(N-Methylcarbamoyl)- β -phenyl- γ -benzoyl- γ -butyrolactone (IVa). A 2-g (5.9 mmole) sample of amide Ia was suspended in 40 ml of glacial acetic acid, 0.33 ml (5.9 mmole) of bromine was added, and the mixture was allowed to stand at room temperature of 7 days. It was then poured into water, and the resulting precipitate was crystallized from ethanol. Lactones IVb and IVc were similarly synthesized.

β -Phenyl- γ -benzoylbutyric Acid (V). A) A mixture of 3 g (8.8 mmole) of amide Ia and 35 ml of 60% H₂SO₄ was refluxed for 1 h, after which it was cooled, and the resulting precipitate was separated and washed successively with water and ether. Crystallization from ethanol gave acid V.

B) A mixture of 1 g (2.9 mmole) of amide Ia and 15 ml of concentrated HBr was refluxed for 3 h. The following day, the precipitate was removed by filtration and crystallized from ethanol to give acid V.

β -Phenyl- γ -bromo- γ -benzoylbutyric Acid (VI). A mixture of 1.5 g (5.6 mmole) of acid V, 25 ml of CH₃COOH, and 0.3 ml (5.6 mmole) of bromine was heated until HBr evolution commenced. When the solution became colorless, it was diluted with water, and the resulting precipitate was removed by filtration and crystallized.

β -Phenyl- γ -benzoyl- γ -butyrolactone (VII). A mixture of 0.5 g (1.4 mmole) of acid VI, 10 ml of 50% ethanol, and 0.05 g of NaOH was refluxed for 10 min, after which the solution was cooled and diluted with water, and the solid was removed by filtration and crystallized from ethanol.

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