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(3-Hydroxy-3-methylbutyn-1-yl)cycloalkan-1-ols in the Ritter Reaction

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Abstract—(3-Hydroxy-3-methylbutyn-1-yl)cycloalkan-1-ols were prepared by the action of (2-lithiooxy-2-methylbutyn-3-yl)lithium on cyclopentanone, cyclohexanone, cycloheptanone, and cyclododecanone. The products react with acetonitrile under Ritter reaction conditions. Therewith, in the presence of 8 g-equiv of sulfuric acid, a 2 : 1 mixture of 1-acetylamino-1-(2-acetylamino-2-methylbutyn-3-yl)cycloalkanes and 1-acetylamino-1-(3-acetylamino-3-methylbutyryl)cycloalkanes is formed, whereas in the presence of 2 g-equiv of the acid, a mixture of 1-acetylamino-1-(2-acetylamino-2-methylbutyn-3-yl)cycloalkanes and 1-acetylamino-1-(3-methyl-2-butenoyl)cycloalkanes in the same ratio.

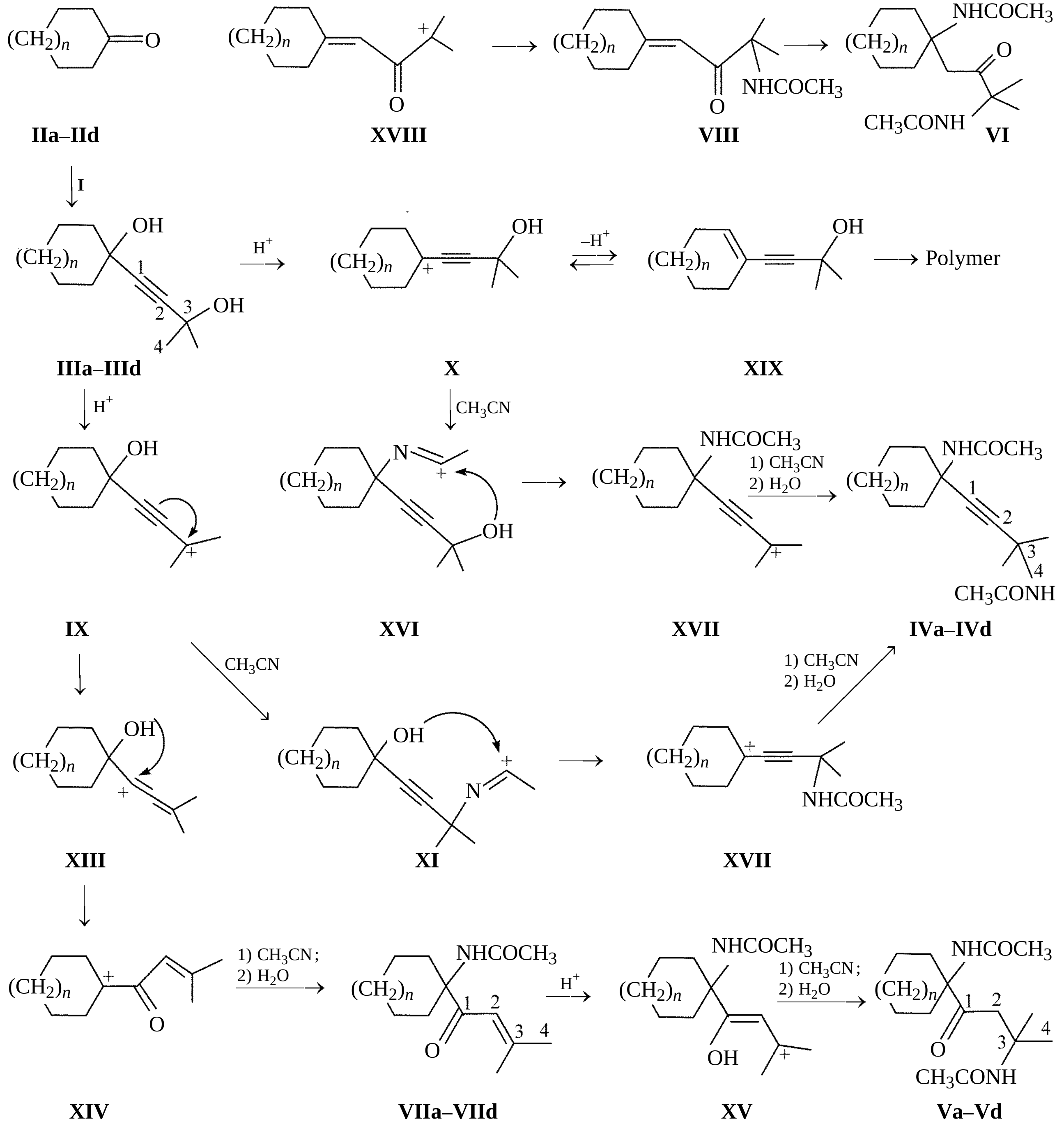
Acetylenic alcohols are widely used in organic synthesis owing to their high reactivity [1–4]. We previously studied transformations of certain ethynylcarbinols under Ritter reaction conditions [5, 6] and found that the reactivity of their triple bond varies over a wide range.

In the present work we dwelt on transformations under Ritter reaction conditions of acetylenic diols, such as (2-hydroxy-2-methylbutyn-3-yl)cyclopentan-, -cyclohexan-, -cycloheptan-, and -cyclododecan-1-ols. It was expected that these compounds would undergo transformations similar to those we observed earlier, since their hydroxy groups each are attached to tertiary carbon located α to the triple bond. Consequently, the resulting carbocations can be stabilized by conjugation with the π-electron system of the triple bond. As we showed in [5], this favors a much faster hydration of the triple bond, under milder conditions, in the absence of mercury catalysts.

Starting diols **IIIa**–**IIId** were prepared by a standard procedure [7] by the action of (3-lithiooxy-3-methylbutyn-1-yl)lithium (**I**) on cycloalkanones **IIa**–**IId** (see scheme and Experimental). The structure of cycloalkanelbutynediols **IIIa**–**IIId** was proved by ^{1}H and IR spectroscopy (Tables 1 and 2).

It was found that the products of the Ritter reaction in the presence of excess sulfuric acid (8 g-equiv), after removal of polymeric admixtures, were two-component mixtures (ratio ~2 : 1). The mixtures were separated by crystallization from ether–ethanol and ether–methanol mixtures. Structural assessment of the major components of the mixtures creates no problems. Since the IR spectra of these compounds contain bands characteristics of amide carbonyl (~1660 cm^{-1}) and NH (~3380 and 1540 cm^{-1}) groups, as well as a very weak band at 2240 cm^{-1} assignable to the triple bond, the major reaction products are 1-acetylamino-1-(3-acetylamino-3-methylbutyn-1-yl)cycloalkanes **IVa**–**IVd** formed by substitution of hydroxy groups in the starting diols by amide, not involving the triple bond (see scheme). The ^{1}H NMR spectra, too, provide evidence for the proposed structures. The spectra contain singlet signals of terminal methyl groups, that appear upfield from the respective signals of the starting diols (by ~1.35 ppm), as well as signals of amide acetyl (two singlets near 1.9 ppm) and two NH groups (Table 2).

The IR spectra of the minor components of the reaction mixtures, too, contain amide vibration bands (Table 1) but lack the C≡C band at 2240 cm^{-1} and contain a band at ~1720 cm^{-1}, characteristic of ketone carbonyl. Obviously, the minor components are amides with hydrated triple bond, and, therewith, only one of the two possible diamidoketones is present (GLC data). The ^{1}H NMR spectra of the isolated diamides show, along with methyl and acetylamino signals (Table 2), two-proton singlets at ~3.1 ppm, characteristic of methylene groups adjacent to carbonyl and amido groups. These spectral data comply with both the possible hydration products, 1-acetylamino-1-(3-acetylamino-3-methylbutyryl)cycloalkanes **V** and 1-acetylamino-1-(3-acetylamino-1-oxo-3-methylbutyl)cycloalkanes **VI**. Structure **V** may be preferred, since the signals of terminal methyl groups are rather upfield (~1.30 ppm), whereas if these groups were adjacent to the carbonyl group, as in compound **IV**, the corresponding signals would have



n = 0 (**a**), 1 (**b**), 2 (**c**), 7 (**d**).

been shifted downfield. Conclusive evidence for the structure of the isolated diamidoketones was obtained chemically. It was found that the Ritter reaction of diols **IIIa**–**IIId** in the presence of 2 g-equiv of sulfuric acid, too, gives a mixture of two amines in a ~2 : 1 ratio, and the major components of the reaction mixtures are identical to diamides **IV** and have a triple bond in the side chain. The minor components of the reaction mixtures were identified, on the basis of ^1H and IR data, as 1-acetylamino-1-(3-methyl-2-butenoyl)cycloalkanes **VIIa**–**VIId**. The IR spectra of compounds **VII** contain bands at ~3375 and 1525 cm^{-1}, characteristic of amide NH groups, as well as an amide carbonyl absorption band at 1660 cm^{-1}. The band at 1680 cm^{-1} relates to absorption of the carbonyl group in α,β-unsaturated ketones and the band

Table 1. Yields, melting points, and IR spectra of compounds **III–V** and **VII**

Comp. no.	Yield, %	mp, °C	IR spectrum, cm^{-1}
IIIa	53	57–59	3275 (OH), 2980, 2940, 2870 (CH), 2240 (C≡C)
IIIb	69	102–104	3350 (OH), 2980, 2855 (CH), 2230 (C≡C)
IIIc	85	122–123	3340 (OH), 2975, 2930, 2855 (CH), 2230 (C≡C)
IIId	82	110–112	3320 (OH), 2935, 2855, 2845 (CH), 2230 (C≡C)
IVa[a]	32	85–87	3380, 3070 (NH), 2955, 2870 (CH), 2240 v.s (C≡C), 1655 v.s (2C=O amide), 1540 (NH)
IVb	34	164–167	3350, 3080 (NH), 2935, 2855 (CH), 2240 v.s (C≡C), 1655 v.s (2C=O amide), 1540 (NH)
IVc	35	134–135	3385, 3070 (NH), 2925, 2855 (CH), 2240 v.s (C≡C), 1660 v.s (2C=O amide), 1540 (NH)
IVd	38	192–194	3400, 3080 (NH), 2930, 2855 (CH), 2240 v.s (C≡C), 1660 v.s (2C=O amide), 1540 (NH)
Va	14	128–130	3380, 3080 (NH), 2955, 2940, 2870 (CH), 1720 s (C=O, ketone), 1660 v.s (2C=O amide), 1540 (NH)
Vb	16	164–165	3360, 3080 (NH), 2940, 2920, 2855 (CH), 1720 s (C=O, ketone), 1660 v.s (2C=O amide), 1540 (NH)
Vc	17	146–148	3390, 3080 (NH), 2945, 2925, 2910, 2855 (CH), 1720 s (C=O, ketone), 1660 v.s (2C=O amide), 1540 (NH)
Vd	18	170–172	3400, 3080 (NH), 2930, 2900, 2855 (CH), 1720 s (C=O, ketone), 1660 v.s (2C=O amide), 1540 (NH)
VIIa	16	151–152	3370 (NH), 2960, 2940, 2870, 2850 (CH), 1680 s (conjud. ketone C=O), 1660 v.s (C=O amidn.), 1620 s (conjud. C=C), 1530 (NH)
VIIb	17	212–213	3360 (NH), 2960, 2940, 2870, 2850 (CH), 1680 s (conjud. ketone C=O), 1660 v.s (C=O amidn.), 1620 s (conjud. C=C), 1530 (NH)
VIIc	18	197–198	3380 (NH), 2960, 2945, 2920, 2870, 2850 (CH), 1680 s (conjud. ketone C=O), 1660 v.s (amide C=O), 1620 s (conjud. C=C), 1525 (NH)
VIId	20	224–225	3375 (NH), 2960, 2950, 2930, 2900, 2860, 2850 (CH), 1680 s (conjud. ketone C=O), 1660 v.s (amide C=O), 1620 s (conjud. C=C), 1525 (NH)

[a] The yields of diamides **IVa–IVd** in reactions with 2 g-equiv of sulfuric acid; the yields in reactions with 8 g-equiv of sulfuric acid are lower by 2–4% because of the slightly stronger polymer formation.

Table 2. ^1H NMR spectra of compounds **III–V** and **VII**, δ, ppm

Comp. no.	Terminal CH_3	CH_2, side-chain CH	H ring	NH, OH	$COCH_3$
IIIa	1.53 s	–	1.51–2.20 m (8H)	2.59 br.s	–
IIIb	1.54 s	–	1.20–1.80 m (10H)	3.08 br.s	–
IIIc	1.52 s	–	1.40–2.20 m (12H)	3.00 br.s	–
IIId	1.51 s	–	1.20–1.95 m (22H)	2.25 br.s, 2.45 br.s	–
IVa	1.35 s	–	2.10–2.30 m (4H), 1.55–1.85m (4H)	5.50 br.s, 5.70 br.s	1.86 s, 1.96 s
IVb	1.35 s	–	2.05–2.20 m (4H), 1.30–1.80 m (6H)	5.56 br.s, 5.80 br.s	1.84 s, 1.99 s
IVc	1.34 s	–	2.10–2.25 m (4H), 1.45–1.80 m (8H)	5.55 br.s, 5.85 br.s	1.83 s, 1.98 s
IVd	1.32 s	–	2.05–2.25 m (4H), 1.30–1.80 m (18H)	5.56 br.s, 5.90 br.s	1.85 s, 1.97 s
Va	1.28 s	3.10 s	2.15–2.40 m (4H), 1.50–1.80 m (4H)	5.50 br.s, 6.10 br.s	1.92 s, 1.97 s

Table 2. (Contd.)

Comp. no.	Terminal CH_3	CH_2, side-chain CH	ring H	NH, OH	$COCH_3$
Vb	1.28 s	3.08 s	2.15–2.30 m (4H), 1.30–1.75 m (6H)	5.60 br.s, 6.16 br.s	1.90 s, 2.00 s
Vc	1.27 s	3.06 s	2.15–2.35 m (4H), 1.40–1.80 m (8H)	5.56 br.s, 6.15 br.s	1.90 s, 2.00 s
Vd	1.26 s	3.05 s	2.10–2.35 m (4H), 1.30–1.80 m (18H)	5.60 br.s, 6.12 br.s	1.92 s, 1.99 s
VIIa	2.14 d, 1.88 d (*J* 1.4 Hz)	6.35 d (*J* 1.4 Hz)	1.70–1.90 m (4H), 1.30–1.50 m (4H)	5.60 br.s	1.99 s
VIIb	2.14 d, 1.88 d (*J* 1.4 Hz)	6.33 d (*J* 1.4 Hz)	1.65–1.85 m (4H), 1.25–1.45 m (6H)	5.55 br.s	1.98 s
VIIc	2.13 d, 1.87 d (*J* 1.4 Hz)	6.31 d (*J* 1.4 Hz)	1.65–1.80 m (4H), 1.25–1.50 m (8H)	5.55 br.s	1.97 s
VIId	2.12 d, 1.87 d (*J* 1.4 Hz)	6.29 d (*J* 1.4 Hz)	1.60–1.80 m (4H), 1.20–1.40 m (18H)	5.45 br.s	1.95 s

at 1620 cm^{-1}, to absorption of its conjugated double bond. The ^1H NMR spectra of the resulting compounds show a multiplet (7 lines; *J* 1.4 Hz) at ~6.30 ppm, assignable to the olefin proton in the α,β-unsaturated fragment, as well as two doublets at ~1.85 and 2.1 ppm, assignable to the methyl groups at the conjugated double bond. The coupling constant of 1.4 Hz relates to allyl coupling between methyl protons and the proton at the side-chain C^2 atom. Signals of one acetylamino group are also observed (Table 2). The above set of signals in the ^1H NMR spectrum corresponds to structure **VII**, since in the case of the alternative amidoketone **VIII**, the signals of terminal methyl groups would appear in a much stronger field, whereas downfield signals would belong to two ring methylene groups located α to the semicyclic double bond.

Obviously, amidoketones **VIIa**–**VIId** obtained in relatively mild conditions convert into diamidoketones **V** in more severe conditions, and it is the latter structure that should be assigned to the above compounds. The formation of such products suggests that water has added by a sterically stronger shielded carbon atom of the triple bond and, consequently, that the reaction is thermodynamically controlled.

It should be noted that the reaction is accompanied by strong polymer formation. This can be explained by the presence of two hydroxy groups in the molecule. It is known [8] that many diols under Ritter reaction conditions give heterocyclic derivatives (oxazoles, oxazines, etc.) via intramolecular reaction of the hydroxy group and the iminium carbocation formed by nitrile addition. Since in our case the side chain contains a triple bond and, therefore, is this strictly linear, the iminium cationic center cannot approach the α,β-hydroxy group, because this requires a substantial distortion of bond angles. As a result, the iminium cation reacts with a "foreign" hydroxy group, giving rise to polymer formation. Evidence for this reasoning comes from the observation in the IR spectrum of the isolated polymeric product (see Experimental) of a broad band near 1660 cm^{-1}, characteristic of N=C–O vibrations. The fraction of this polymer gets smaller if more solvent is used to perform the reaction (16–20-fold excess of acetonitrile with respect to substrate). The other, smaller fraction of the polymer, whose IR spectrum contains no such band, results, as will be shown below, from polymerization of (2-hydroxy-2-methylbutyn-3-yl)cycloalkenes formed by dehydration of the starting diols.

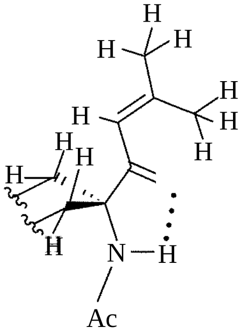
Since the fraction of nonhydrated compounds **IV** in the reaction mixture is independent of the amount of sulfuric acid, we can suggest that the triple bond in amides **IV** undergoes no direct hydration; otherwise, the fraction of compounds **V** obtained in more severe conditions would be smaller. These suggestions allow us to propose the above scheme.

Since the hydroxy groups in diols **III** have similar environments, protonation and subsequent elimination of each of them to give cations **IX** or **X**, respectively, should occur at comparable rates. Cation **IX** with the positive charge in the side chain can transform along two different pathways. In the first case, it takes up a nucleophile molecule to form intermediate **XI** which transforms into cation **XII** via migration of the hydroxy group to the iminium cationic center. The latter takes up a further acetonitrile molecule and is hydrated to give the major reaction product, unsaturated diamide **IV**. In the second case, conjugation of the cationic center of intermediate **IX** with the triple bond induces the positive charge on C^4. The migration of the hydroxy group to this atom, like that observed in the Meyer–Schuster rearrangement [3], provides enone cation **XIV**. Addition to latter of an acetonitrile molecule followed by hydration gives rise to amidoketone **VII** that, in mild reaction conditions, is the final reaction product. In the presence of excess sulfuric acid, the enone fragment undergoes protonation to form intermediate **XV** whose transformations lead to diamidoketone **V**.

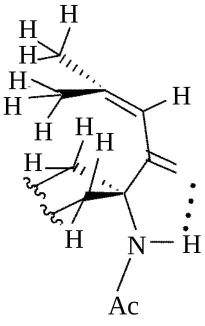
Cation **X** formed by elimination of the other hydroxy group, too, can transform into diamide **IV** via intermediates **XVI** and **XVII** that are similar to ions **XI** and **XII**. It might be expected that the rearrangement of cation **X**, similar to that described above, would give enone ion **XVIII** with a semicyclic double bond, and further amidoketones **VIII** and **VI**. However, as mentioned above, no expected compounds formed under the reaction conditions.

The explanations for this seemingly strange result can be found in the properties of diols **III**. When synthesized these compounds we found that they are extremely susceptible to dehydration into conjugated enynes **XIX**. Thus, in particular, on attempted vacuum distillation at ~80°C cyclopentane diol **IIIa** dehydrated by more than 50%. Probably, under our reaction conditions, the stabilization of cyclic carbocation **X** by proton expulsion and formation of enyne **XIX** proves thermodynamically more favorable than its isomerization into ion **XVIII**, which explains the lack among the reaction products of amides **VI** or **VIII**. At the same time, enyne **XIX** which is chemically equivalent to diol **III** as a substrate of the Ritter reaction partially transforms into diamide **IV** as a result of the reversibility of protonation–deprotonation and partially, most likely, polymerizes to form the less polar fraction of the polymeric products. The IR spectrum of these polymeric products lacks the band at ~1660 cm^{-1}, implying that they do not result from intermolecular reaction of iminium intermediates with alcohols.

It should be noted that the enone fragment in amidoketones **VIIa**–**VIId** has an *S-cis* configuration, as evidenced by the roughly equal intensities of the C=O and C=C absorption bands (~1680 and 1620 cm^{-1}) in their IR spectra and the relatively low intensity of the first of these bands (much lower than the intensity of the amide carbonyl band at 1660 cm^{-1}) [9]. The proposed steric structure is consistent with the ^1H NMR spectra of compounds **VIIa**–**VIId**: The signal of one of the methyl groups appears strongly downfield, implying proximilty of this group to carbonyl. Such configuration of amidoketones **VIIa**–**VIId** is explained by steric factors. As seen from the proposed scheme, has the *S-trans* configuration been realized, the van der Waals radii of terminal methyl and ring α,α'-methyl groups would have overlapped.



S-cis-**V**



S-trans-**V**

Thus, owing the possibility of conjugation between the cationic center and the triple band, the Ritter reaction of diols **IIIa**–**IIId** involves, along with the simple substitution of the hydroxy groups by amide, hydration of the triple bond. The latter process is made possible by the isomerization of the γ-hydroxyproparyl carbocation into α-enone. Obviously, the ratio of nonhydrated products **IV** and hydrated products **V** or **VII** is determined by the relative rates of nucleophilic addition and isomerization, which explains why this ratio only slightly depends on the amount of acid.

EXPERIMENTAL

The IR spectra were measured on a Nicolet Protege-460 Fourier spectrometer. The ^1H NMR spectra were obtained on a Tesla BS-567 spectrometer (100 MHz), solvent $CDCl_3$, internal reference HMDS. The reaction progress and product purity were controlled by GLC on Chrom-5, stainless-steel column (2000 × 2 mm), packing Apiezon L on Chromaton N-AW-DMCS (0.16–0.20).

(3-Hydroxy-3-methylbutyn-1-yl)cycloalkan-1-ols *(general procedure).* A solution of 70 mmol of BuLi in hexane was slowly added with vigorous stirring under argon to a solution of 35 mmol of anhydrous 2-methylbut-3-yn-2-ol in 100 of THF cooled to –30°C. After 1-h stirring, 25 mmol of ketone was added, and stirring was continued for an additional 3 h. The temperature of the reaction mixture was gradually raised to ambient, after which the reaction mixture was left to stand overnight. The alcoholates that formed were decomposed with caution with water and then 300 ml of water was added. The mixture was treated with ether. The extracts were washed with water and dried with $CaCl_2$. The solvent was removed, and the products were purified by recrystallization from hexane.

Ritter reaction. Concentrated sulfuric acid, 1.2 or 4.6 ml, was slowly added with cooling (5–10°C) to a solution of 10 mmol of diol in 20 ml of acetone. The temperature of the reaction mixture was gradually (over the course of 3–4 h) raised to ambient, and stirring was continued until the reaction was complete (control by GLC). The reaction mixture was then poured with caution to excess aqueous ammonia, treated with ether (a greater volume of the extractant was used, since amidoketones **V** and **VII** are sparingly soluble in ether), and the extracts were dried with $MgSO_4$. The solvent was removed to leave a mixture that contained up to 50% of polymers. Hexane was added to the residue to dissolve most low-polar polymer (polymerized enynes **XIX**). The solution was decanted, and the residue was dissolved in ethanol. Undissolved part (polymer formed by an intermolecular Tielmans reaction) was filtered off. The filtrate was passed through a bed of silica gel (Chemapol L 40/100) to remove residual polymer. The resulting alcoholic solution that contained a mixture of diamide **IV** and diamidoketone **V**, or diamide **IV** and amidoketone **VII** in a 2:1 ratio was concentrated in a vacuum to 5–6 ml and then diluted with ether with causion. Products **V** and **VII** that are poorly soluble in ether precipitated. Therewith, amidoketones **Vb**–**Vd** and **VIIb**–**VIId** were isolated as individual crystalline substances. Compounds **Va** and **VIIa** were isolated as thick oily substances with a considerable admixture of diamide **IVa**. This oil was dissolved in a minimum of dry methanol, and pure compounds **Va** and **VIIa** were obtained by reprecipitation with ether. The mother liquors that contained butynyldiamides with admixtures **V** or **VII** were evaporated to dryness, dissolved in a minimum of absolute ethanol, the admixtures were separated by repeated treatment with ether, and the residues were evaporated and subjected to a vacuum. Thus obtained diamide **Va** was a thick oil that gradually crystallized on standing. The other diamides drop as white crystals. If required, they were further purified by recrystallization from ethanol.

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