# Formation of 1,2,3-Triazoles, Secondary Amides, α-Aminoketones, and Vinylketones in the Acid-catalyzed Decomposition of 5-Hydroxy-$\Delta^2$-1,2,3-Triazolines

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On treatment with acid 5-hydroxy-$\Delta^2$-1,2,3-triazolines are converted into 1,2,3-triazoles, amides, α-aminoketones, or vinylketones, depending on the substituents. Aliphatic diazonium ions are proposed as intermediates in the last three cases.

Nucleophiles, such as benzoyl chloride or $BF_3/CH_2N_2$, react at N-3, giving derivatives of the corresponding ketotriazenes.

As described previously [1-4] 5-hydroxy-$\Delta^2$-1,2,3-triazolines undergo various conversions on treatment with base. Acid also induces reactions which may be rather vigorous. The products are

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(Scheme 1) 1,2,3-triazoles (IV), amides (XIII), α-aminoketones (VIII), or vinylketones (XI). In a number of experiments, one equivalent of trifluoroacetic acid (TFAA) was added to a 0.2 M solution of the hydroxytriazoline in $CDCl_3$. The product distribution as determined by ^{1}H NMR spectroscopy is shown in Table 1. Here is also given the yields obtained in some other experiments where the products were isolated and identified after treatment of the solid triazoline or a solution of it in an organic solvent with hydrochloric acid.

*Formation of 1,2,3-triazoles (IV).* With the exception of case v, 1,2,3-triazoles are only
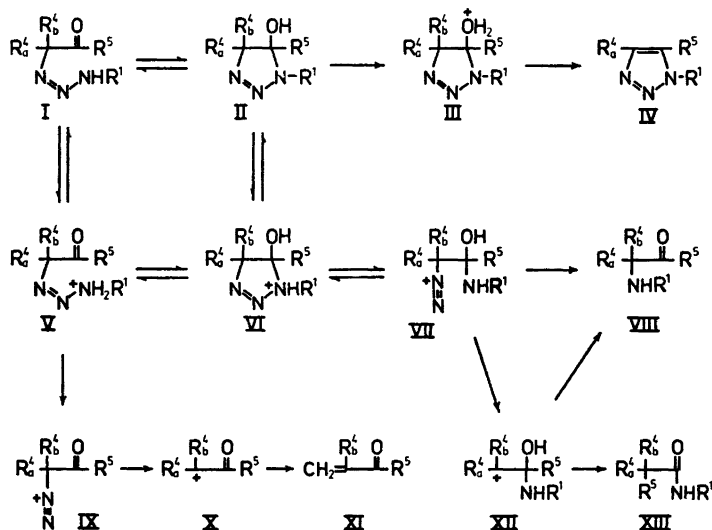


*Scheme 1.*

*Table 1.* Product distributions in acid-catalyzed decompositions of 5-hydroxy-$\Delta^2$-1,2,3-triazolines, II (or α-ketotriazenes, I).

| Case | Substituents | | | | Products detected by NMR (CDCl₃/TFAA) | | | | Isolated products (aqueous acid) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $R^1$ | $R_b^4$ | $R_a^4$ | $R^5$ | IV | XIII | VIII | XI | IV | XIII | VIII | Procedure |
| a | Me | H | Me | Me | 22 | 79 | | | | | | |
| b | Me | H | Me | iPr | 42 | 53 | | | | | | |
| c | Me | H | Me | tBu | 33 | 47 | | | | 35 | | B |
| d | Me | H | $-(CH_2)_4-$ | | 66 | | | | 25 | 43 | | B |
| e | Me | H | Me | Ph | 5 | 90 | | | | 97 | | B |
| f | Me | Me | Me | iPr | | 32 | 34 | 16 | | | | |
| g | Me | Me | Me | tBu | | 26 | 38 | 10 | | | | |
| h | Me | Me | Me | Ph | | | | | | 97 | | B |
| i | $PhCH_2$ | H | H | Me | 52 | | 44 | | | | | |
| j | $PhCH_2$ | H | H | Ph | 12 | 33 | 41 | | | | | |
| k | $PhCH_2$ | H | Me | Me | 20 | 75 | | | | | | |
| l | $PhCH_2$ | H | Me | Et | | | | | | 94 | | D |
| m | $PhCH_2$ | H | Me | iPr | 43 | 50 | | | | | | |
| n | $PhCH_2$ | H | Me | tBu | 30 | 63 | | | | | | |
| o | $PhCH_2$ | H | $-(CH_2)_4-$ | | 83 | 13 | | | 77 | 15 | | C |
| p | $PhCH_2$ | H | Me | Ph | 5 | 91 | | | | | | |
| q | $PhCH_2$ | Me | Me | iPr | | 27 | 28 | 24 | | 32 | 62 | D |
| r | Ph | H | Me | Me | <1 | 96 | | | | 93 | | D |
| s | Ph | H | Me | Et | | | | | | 97 | | B |
| t | Ph | H | Me | iPr | <1 | >90 | | | | | | |
| u | Ph | H | Me | tBu | <1 | 55 | | | | 49 | 14 | C |
| v | Ph | H | $-(CH_2)_4-$ | | <1 | | | | 15 | 46 | | C |
| w | Ph | H | Me | Ph | <1 | 94 | | | | | | |
| x | Ph | Me | Me | iPr | | 36 | 27 | 33 | | 47 | 31 | A |
| y | Ph | Me | Me | tBu | | | | 89 | | | | |
| z | Ph | Me | Me | Ph | | 97 | | | | 100 | | B |
| ü | $pNO_2Ph$ | Me | Me | iPr | | | | | | 40 | 36 | C |
| ö[a] | Ts | Me | Me | iPr | | | | | | 63 | 7 | |

[a] This triazoline decomposes spontaneously.

formed in a significant amount when $R^1$ is aliphatic. On the other hand the size of $R^1$ does not seem to influence the yields, as they are almost the same when $R^1$ is methyl and benzyl (*cf.* cases a and k, b and m, c and n, e and p). This is in contrast to the influence of $R^5$, where the yield of triazole increases in the series Ph, Me, *t*-Bu, iPr, $-(CH_2)_4-$ for a given alkyl group at N-1.

The yield of triazole is relatively high when the triazoline is unsubstituted at C-4 (*cf.* cases i and j with cases k and p).

The effect of the solvent has only been examined in case a. The yield of 1,4,5-trimethyl-1,2,3-triazole was almost the same in chloroform, benzene, methanol, and dimethyl sulfoxide, whereas it was more than doubled in pyridine (55 %).

From a synthetic point of view the formation of 1,2,3-triazoles is of limited value, since dehydration of hydroxytriazolines is normally better accomplished by treatment with methanolic potassium hydroxide.[3] Only when the groups to be eliminated (H and OH) are prevented from being *trans* to each other (cases d, o, and v) the acid catalyzed dehydration may be valuable.

*Formation of amides (XIII), α-aminoketones (VIII), and vinylketones (XI).* Amides are formed in almost all cases, most often as the main product. Hence, this reaction provides a realistic synthetic route to highly branched

carboxylic acids by way of their amides, particularly when $R^1$ is aromatic. With regard to $R^5$ the yield of amide follows the reverse trend of that observed for the triazole formation.

Formation of α-aminoketones and vinylketones only takes place in a few instances and is therefore less important.

The reactions in question are closely related to the spontaneous decomposition of 1-tosyl-$\Delta^2$-1,2,3-triazolines (cf. references in Ref. 4). Accordingly, the tert-butoxide-catalysed reaction of tosyl azide with diisopropyl ketone (case ö) gives a mixture of XIII and VIII by way of the triazoline.

*Proposed mechanism for the acid-catalyzed conversions of 5-hydroxy-$\Delta^2$-1,2,3-triazolines.* The proposed mechanism for the acid-catalyzed conversions of hydroxytriazolines is outlined in Scheme 1. Although the triazoline nucleus in the presence of acid is most likely to be protonated at N-3 (cf. the section on reactions with other nucleophiles), this is not shown in the scheme because it does not manifest itself by starting irreversible processes. In contrast, protonation at N-1 may cause ring-opening to give the aliphatic diazonium ion VII and subsequently XIII and VIII by elimination of nitrogen and migration of a group from C-5 to C-4.

The higher yield of products (XIII and VIII) derived from VII relative to that of triazole, when $R^1$ is aromatic rather than aliphatic, is in accordance with the supposition that the ring-opening is reversible with the equilibrium lying more to the right in the former case.

An unsettled question, which is closely related to the long standing discussion of the mechanism for the reaction of aliphatic amines with nitrous acid,[5-7] is whether the diazonium ion (VII) or the carbocation (XII) is the branching point for further reactions, i.e. whether migration of the C-5 group takes place concerted with or after elimination of nitrogen.

The concerted mechanism presumably applies when there are two hydrogens at C-4. This will explain the high yield of VIII relative to XIII in cases i and j (cf. Ref. 8, concerning 5-alkoxytriazolines). The relatively high stability of primary diazonium ions (VII, $R_a^4 = R_b^4 = H$) assumingly demands intramolecular assistance – at which the amino group is most effective[9] – in the expulsion of nitrogen.[10] This theory is

in accordance with the concurrent high yield of IV ($R_a^4 = Me$ reduces it to less than half). Not decomposing spontaneously into XII, VII has the possibility of reverting to the closed structure, VI, and eventually end up as IV, if it misses conversion into VIII.

In contrast, with two methyl groups present at C-4, decomposition of VII will lead to a tertiary carbocation, XII ($R_a^4 = R_b^4 = Me$). Hence the non-concerted mechanism would be expected in this case. The relatively high yield of VIII in cases f, g, q, and x must here be due to steric hindrance toward migration of the bulky $R^5$ in XII.

With only one methyl group at C-4 the situation is less clear. The stereochemistry of the acid-catalyzed conversion of II into XIII was studied in case s. IIs – like some other hydroxytriazolines – forms a racemic mixture on crystallization and could hence be obtained in optically active form by mechanical separation of the two kinds of crystals. Treatment of the levorotatory form with TFAA gave (+)-XIIIs of the same optical purity as the starting material. Thus the reaction is completely stereospecific and presumably involves inversion at C-4.[7] However, this does not differentiate clearly between the two mechanisms, since inversion may result from the $S_N2$-like reaction in the concerted mechanism as well as from steric control of the carbocation conformation in the two-step mechanism.[7]

Vinylketones, XI, are formed from sterically encumbered triazolines with two methyl groups at C-4. They are most likely formed by way of the protonated triazene, V, which may be generated either by protonation of the ketotriazene, I, or, when $R^1$ is aliphatic, more likely by cleavage of the N-1···C-5 bond of the protonated triazoline, VI. On deamination, V leads to a tertiary α-ketodiazonium ion, IX, which is apt to loose nitrogen spontaneously[11] to give the carbocation X and finally the vinylketone. XI.

The trend in the yield of triazole from 1,5-dialkyltriazolines largely follows the capability of $R^5$ at hindering protonation of N-1, which would lead to XIII or VIII. For instance the accessibility of N-1 in the 4,5-tetramethylene triazolines (cases d, o, and v) in the assumed envelope conformation[12] is particularly poor, and protonation of the hydroxy group, leading
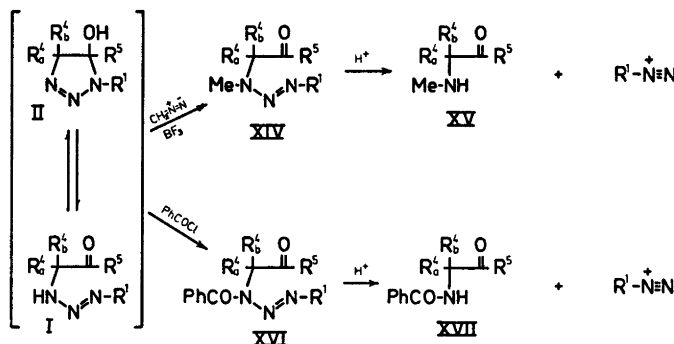
Scheme 2.

to dehydration, is therefore strongly favored.

The increased yield of triazole when running the reaction in pyridine may be related to this phenomenon. Thus it may be more difficult for the large proton donor (*cf.* Ref. 13) in this solvent to reach the rather hindered N-1 lone-pair than the more exposed axial hydroxyl group.

*Reaction of 5-hydroxy-Δ²-1,2,3-triazolines with other electrophiles.* Also electrophiles other than protons will react with the triazolines (Scheme 2). Thus treatment of II 1, s, and x with diazomethane and boron trifluoride in ether[14] gave products whose structure appeared to be that of methylated ketotriazenes (XIV). The position of the methyl group, N-3 rather than N-1, follows from the fact that for example the product formed in case 1, on treatment with boiling hydrochloric acid,[15] gives a mixture of benzyl alcohol, benzyl chloride, and the α-aminoketone XVI. Besides, the product formed in case x, XIVx, could be synthesized by coupling the α-aminoketone XVx with phenyl diazonium chloride (*cf.* Ref. 15, p. 695).

Benzoylation in pyridine of 5-hydroxy-Δ²-1,2,3-triazolines (again represented by cases 1, s, and x) normally gives the corresponding benzoylated ketotriazene, XVI. The structure appears from the NMR and IR spectra (two C=O bands present in the product in cases 1 and s) and from the fact that benzoylated α-aminoketones (XVII) are obtained on treatment of the benzoyl derivatives, XVI 1 and x, with acid.

Benzoylation of IIf followed by treatment with sulfuric acid gave, by way of XVIf, the benzoylated α-aminoketone XVIIf (identical with XVIIx) in a 49 % yield. *N*-Methyl-benzamide, the product to be expected if

reaction occurred at N-1, could not be detected.

The methyl and benzoyl derivatives might of course come from the ketotriazene (only one of the two possible tautomeric forms is shown in Scheme 2). However, if this were the case, one would expect reaction to occur also at N-1, at least when both substituents of the triazene are aliphatic. In case f, reaction at N-1 should even be greatly favored — for steric reasons — but still only reaction at N-3 is observed.

An explanation to the exclusive formation of N-3 derivatives would be that it is the triazoline (II), and not the ketotriazene itself, that reacts with the electrophilic reagent. Thus the positive charge generated in II in the electrophilic attack will be much more effectively delocalized when reaction takes place at N-3 rather than at N-1.

## EXPERIMENTAL

NMR-spectra were recorded on Varian A-60 and JEOL JNM-C-60HL instruments, using TMS as an internal standard (CDCl$_3$ if not otherwise specified). IR-spectra were recorded on a Perkin-Elmer model 421 instrument. Preparative thin-layer chromatography (TLC) was carried out using Merck Kieselgel PF$_{254}$. Melting points are uncorrected. All hydroxy-triazolines have been described in previous papers. Other starting materials are commercially available. Microanalyses were performed by Dr. A. Bernhardt, Mikroanalytisches Laboratorium.

*Decomposition by TFAA of 5-hydroxy-Δ²-1,2,3-triazolines in CDCl$_3$ and determination of the product distribution by NMR spectroscopy* (*cf. Tables 1 and 3 − 6*). 0.1 mmol of triazoline is dissolved in 0.5 ml of CDCl$_3$, and 0.1 mmol (7.6 μl) of TFAA is added. Heat generation is considerable when the N$_2$ evolution is so. 0.1 mmol (10.5 μl) of 1,1,2,2-tetrachloroethane is added to provide a quantitative internal

standard, and the mixture is shaken with saturated NaHCO₃. The NMR spectrum is recorded and integrated and the yields are calculated from the relative signal intensities of products and $CHCl_2CHCl_2$.

$\delta$-Values of signals from compounds in parenthesis in Tables 3 – 6 have been read directly from the NMR spectra of the reaction mixtures after shaking with NaHCO₃. These compounds have not been isolated.

The same procedure, except for the treatment with NaHCO₃, was used in the decomposition of IIa in benzene, dimethyl sulfoxide, and pyridine. In methanol it proved necessary to first remove the solvent (with compressed air) due to interference of the OH and reference signals. HCl in ether was first added in order to prevent loss of triazole. After neutralization (NaHCO₃) and dissolution in CDCl₃, standard was added and the NMR spectrum recorded.

*Acid-catalyzed decompositions of 5-hydroxy-Δ²-1,2,3-triazolines and isolation of the products (Tables 1 – 6). Procedure A* (case x) The hydroxytriazoline (*ca.* 2 mmol) is added to 5 ml of ice cold 3 N hydrochloric acid. The mixture is stirred for half an hour at 0 °C and then for half an hour at room temperature. The precipitated amide (XIII) is filtered off and recrystallized from ethyl acetate-pentane.

The filtrate is neutralized with NaHCO₃ and extracted with ether; the extract is dried over MgSO₄. Evaporation and recrystallization from pentane gives the α-aminoketone (VIII).

*Procedure B* (cases c, d, e, h, s, and z). The hydroxytriazoline (1 – 2 mmol) is dissolved in 10 ml of methylene chloride, and 2 ml of 3 N hydrochloric acid is added. The mixture is shaken for a few minutes, until the evolution of nitrogen has ceased. The aqueous phase is washed with 4 ml of methylene chloride (plus 2 × 5 ml in case d). The combined organic phases are dried over MgSO₄ and evaporated. The amide (XIII) is usually left in a very pure state. It may be recrystallized from ethyl acetate-pentane (or cyclohexane in case z).

In case d the triazole, IVd, is obtained from the aqueous phase after neutralization (NaHCO₃) and extraction with methylene chloride. It is purified by way of its picrate, which is recrystallized from ethanol.

*Procedure C* (cases o, u, v, and ü). The hydroxytriazoline (1 – 2 mmol) is dissolved in 10 ml of methylene chloride, and 1 ml of 3 N hydrochloric acid is added. The mixture is shaken for a few minutes and then neutralized with NaHCO₃ and extracted with methylene chloride. After drying (MgSO₄) and evaporation, the resulting mixture is subjected to TLC

*Table 2.* Melting points and analyses of isolated products.

| Structure | Case | M.p. Found | Reported | Formula | Analyses Found C | H | N | Calc. C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| IV | d(picrate) | 157 – 59 | | $C_{13}H_{14}N_6O_7$ | 42.47 | 3.99 | 23.10 | 42.62 | 3.86 | 22.94 |
| | o | 79 – 80 | 77[16] | $C_{13}H_{15}N_3$ | 73.17 | 7.15 | 19.63 | 73.23 | 7.09 | 19.63 |
| | v | 112 – 13 | 117 – 18[17] | $C_{12}H_{13}N_3$ | 72.30 | 6.55 | 21.32 | 72.35 | 6.57 | 21.10 |
| XIII | c | 85 – 86 | | $C_8H_{17}NO$ | 67.30 | 12.04 | 9.74 | 67.10 | 11.96 | 9.79 |
| | d | 50 – 53 | 58 – 59[18] | | | | | | | |
| | e | 78 – 80 | | $C_{10}H_{13}NO$ | 74.30 | 8.20 | 8.75 | 73.59 | 8.03 | 8.58 |
| | h | 64 – 65 | | $C_{11}H_{15}NO$ | 74.72 | 8.64 | 8.06 | 74.51 | 8.52 | 7.90 |
| | l | 45 – 46 | 47.5 – 48.5[19] | | | | | | | |
| | o | 94 – 95 | | $C_{13}H_{17}NO$ | 76.73 | 8.32 | 7.03 | 76.80 | 8.43 | 6.89 |
| | q | 44 – 45 | | $C_{14}H_{21}NO$ | 76.50 | 9.54 | 6.32 | 76.68 | 9.65 | 6.39 |
| | r | 102 – 102.5 | 105.5[20] | | | | | | | |
| | s | 109 – 110 | 110 – 110.5[21] | | | | | | | |
| | u | 109 – 110 | 104.5[22] | | | | | | | |
| | v | 159 – 160 | 160[23] | | | | | | | |
| | x | 78 – 79 | 78 – 79[24] | | | | | | | |
| | z | 99 – 100 | | $C_{16}H_{17}NO$ | 80.46 | 7.25 | 6.03 | 80.30 | 7.16 | 5.86 |
| | ü | 119 – 120 | | $C_{13}H_{18}N_2O_3$ | 62.25 | 7.12 | 11.02 | 62.37 | 7.25 | 11.19 |
| | ö | 160 – 164 | | $C_{14}H_{21}NO_3S$ | 59.18 | 7.35 | 4.82 | 59.33 | 7.47 | 4.94 |
| VIII | q(hydrochloride) | 196 – 204 | | $C_{14}H_{22}NOCl$ | 65.50 | 8.58 | 5.39 | 65.73 | 8.67 | 5.47 |
| | u(benzoylated) | 91 – 93 | | $C_{20}H_{23}NO_2$ | 77.78 | 7.48 | 4.75 | 77.63 | 7.49 | 4.53 |
| | x | 65 – 66 | | $C_{13}H_{19}NO$ | 75.97 | 9.38 | 6.70 | 76.05 | 9.33 | 6.82 |
| | ü | 163 – 164 | | $C_{13}H_{18}N_2O_3$ | 62.26 | 7.41 | 11.03 | 62.37 | 7.25 | 11.19 |
| | ö | 155 – 156 | | $C_{14}H_{21}NO_3S$ | 59.24 | 7.32 | 4.98 | 59.33 | 7.47 | 4.94 |
| XI | y | liq. | | $C_8H_{14}O$ | | | | 76.13 | 11.18 | |

*Table 3.* NMR data of amides (XIII). Compounds in parentheses have not been isolated; the NMR data were obtained directly from the reaction mixtures after shaking with saturated NaHCO$_3$ solution. The coupling constant between CONH and the adjacent CH$_3$ or PhCH$_2$ protons is 4−6 Hz.

| | R¹ | | R$_b$⁴ | R$_a$⁴ | R⁵ | |
|---|---|---|---|---|---|---|
| (a) | 2.82d | | 2.40 sept. | | 1.16d | |
| (b) | 2.84d | | | 1.12d | 0.90d | |
| c | 2.78d | | 2.07q | 1.09d | 0.97s | |
| d | 2.83 broad s | | 2.1−2.9 m | | 1.5−2.2 m | |
| e | 2.73d | | 3.56q | 1.53d | 7.3"s" | |
| (f) | 2.80d | | | 1.08s | 0.85d | |
| (g) | 2.79d | | | | | |
| h | 2.73d | | | 1.59s | 7.37"s" | |
| (j) | 4.39d | 7.28s | | 3.60s | 7.0−7.5m | |
| (k) | 4.45d | 4.50s | 2.52sept. | 1.19d | | |
| l | 4.44d | 7.30s | | 1.14d | 0.7−2.4m | |
| (m) | 4.45d | | | | | |
| (n) | 4.43d | | 1.98q | 1.07d | 0.97s | |
| o | 4.41d | 7.28s | 2.1−3.0m | | 1.3−2.2m | |
| (p) | 4.39d | | 3.61q | 1.55d | | |
| q | 4.44 | 7.30s | | 1.08s | 0.84d | 2.02 sept. |
| r | 7.0−7.7m | | 2.54sept. | 1.24d | | |
| s | 6.9−8.0m | | | 1.21d | 0.7−2.6m | |
| (t) | 7.0−7.7m | | | 1.20d | 0.97d | 0.99d |
| u | 6.9−7.7m | | 2.15q | 1.22d | 1.04s | |
| (w) | 6.9−7.7m | | 3.85q | 1.62d | | |
| x | 6.9−7.8m | | | 1.21s | 0.92d | 2.08sept. |
| z | 6.9−7.6m | | | 1.66s | | |
| ü | 7.78"d" | 8.26"d" | | 1.24s | 0.94d | 2.08sept. |
| ö | 7.39"d"8.02"d"2.47s | | | 1.04s | 0.74d | 1.85sept. |

*Table 4.* NMR data of α-aminoketones (VIII) (*cf.* comments to Table 3).

| VIII | R¹ | R$_b$⁴ | R$_a$⁴ | R⁵ |
|---|---|---|---|---|
| (f)ᵃ | 2.26s | | 1.28s | 1.07d |
| (g) | 2.21s | | 1.25s | 1.14s |
| (i) | 3.52s? | | 3.79s? | 2.12s |
| q | 3.59s, 7.3−7.7m | | 1.37s | 1.11d, 3.32sept. |
| u | 6.5−7.4m | 4.66q | 1.32d | 1.20s |
| benzoy-lated u | 7.0−7.7m | 5.80q | 1.13d | 1.35s |
| x | 6.4−7.3m | | 1.49s | 1.03d, 3.39sept. |
| ü | 6.54"d", 8.10"d" | | 1.58s | 1.06d, 3.29sept. |
| ö | 7.30"d", 7.81"d", 2.42s | | 1.46s | 1.08d, 3.13sept. |

ᵃ *Cf.* data for 2-methylamino-2,4-dimethyl-3-pentanone (*v.i*).

(eluents: case o: ether-pentane 2:1; case u: ethyl acetate-pentane 1:6; case v: ethyl acetate-pentane 1:2; case ü: ethyl acetate-pentane 1:3). The products are recrystallized from ethyl acetate-pentane, VIIIu after benzoylation in pyridine.

*Procedure D* (cases l, q, and r). The hydroxy-triazoline (1−2 mmol) is dissolved in 10 ml of ether, and 0.3 ml of 3 N hydrochloric acid is added. The mixture is shaken for a few minutes until evolution of nitrogen has ceased. The amide, XIII, is left when the dried (MgSO$_4$) ether phase is evaporated.

In case q, the ether phase was first washed with 3 × 4 ml of 3 N hydrochloric acid, and the amide was recrystallized from cyclohexane-pentane. The combined aqueous phases were neutralized with NaHCO$_3$ and extracted with

*Table 5.* NMR data of vinylketones (XI) (*cf.* comments to Table 3).

| XI | $CH_2=C{<}$ | $R_b{}^4$ | $R^5$ |
|---|---|---|---|
| (f,q,x) | 5.79m, 5.97m | 1.89m | 1.10d |
| y,(g) | 5.40m | 1.91m | 1.24s |

methylene chloride. Drying and evaporation gave the α-aminoketone, VIIIq, which was converted into its hydrochloride by HCl in ether.

*Decomposition of Iy by TFAA in chloroform.* Iy (0.433 g) dissolved in 10 ml of chloroform was decomposed by 0.15 ml of TFAA. The reaction mixture was washed with 10 ml of 4 N hydrochloric acid, dried over MgSO₄, and evaporated at 60 mmHg. Distillation yielded 0.193 g (87 %) of the vinylketone, XIy. Owing to the presence of a trace of chloroform a satisfactory elementary analysis could not be obtained. In the mass spectrum, however, the molecular ion was present at 126 *m/e.*

*Reaction of tosyl azide with diisopropyl ketone.* Diisopropyl ketone (1.42 ml, 0.01 mol) was added to a solution of 0.5 g of potassium in 10 ml of *tert*-butyl alcohol. Tosyl azide [25] (1.55 ml) was added dropwise and with stirring and cooling so that the temperature did not exceed 30 °C. Stirring was continued for 4 min. The mixture was poured into 200 ml of ice-water, whereby considerable nitrogen evolution occurred. The mixture was extracted with 4 × 25 ml of methylene chloride; it was necessary to let the mixture stand overnight for separation the first time. The extract was dried over MgSO₄ and evaporated. A semisolid mixture was left, which was converted into a colorless, crystalline product, VIIIö, on trituration with ether-pentane. Yield: 191 mg (7 %), m.p. 147−151 °C. Recrystallization from ethyl acetate two times gave the pure product (*cf.* Table 2 for m.p. and analysis and Table 4 for NMR data).

Acidification of the aqueous phase with hydrochloric acid caused precipitation of 1.78 g (63 %) of XIIIö as slightly discolored crystals, which were recrystallized from ethyl acetate (*cf.* Table 2 for m.p. and analysis and Table 3

for NMR data). The structure of XIIIö was confirmed by its conversion into p-toluene-sulfonamide and 2,2,3-trimethylbutanoic acid on hydrolysis: 97 mg of XIIIö was heated to 100 °C for a few minutes with a mixture of 0.2 ml of water and 0.4 ml of conc. sulfuric acid, until the mixture became clear. The reaction mixture was extracted with pentane (3 × 3 ml). The extract was washed with water, dried over MgSO₄, and evaporated, leaving 43 mg (96 %) of 2,2,3-trimethylbutanoic acid as low melting crystals. NMR data: 0.90 (d, 6 H), 1.12 (s, 6 H), and 2.02 (sept., 1 H). Water (1 ml) was added to the inorganic phase, causing crystal-lization of 42 mg (72 %) of *p*-toluenesulfonamide, identified through mixed melting point with an authentic sample.

*Treatment of optically active IIs with TFAA.* Some hydroxytriazolines crystallize as a racemic mixture and may hence be obtained in optically active form by mechanical separation of (+)- from (−)-crystals. Slow evaporation of a solution of IIs in ether dried over sodium produced single crystals weighing up to 2 mg. The individual crystals were visually in-distinguishable, and in order to separate (+)- from (−)-crystals the rotation of each crystal had to be measured. In several cases [α]_D 199° (*c, ca.* 0.1 in acetone) was measured, and this value is therefore considered to apply for optically pure IIs. The specific rotation was often lower due to the presence of twins.

A larger amount of optically active IIs was obtained by cooling a saturated ethereal solution. The resulting crystal aggregates were sorted according to sign of rotation in acetone. After collecting a sufficient amount, recrystal-lization of the (−)-fraction from ether-pentane gave a specific rotation of −188.3°, correspond-ing to an optical purity of 95 %. 17.4 mg of this material was dissolved in *ca.* 1 ml of CDCl₃, and 10 μl of TFAA was added. The reaction was completed after a few seconds. After a few minutes the solution was evaporated and the residue subjected to TLC (ethyl acetate-pentane 1:6), resulting in 15.3 mg of pure XIIIs. The specific rotation was +37.9° (*c,* 1.5 in acetone), corresponding to an optical purity of 96 %.[26] Thus the reaction seems to be completely stereospecific.

*Methylation of 5-hydroxy-$\Delta^2$-1,2,3-triazolines* (*cf. Tables 7 and 8*). The triazoline (2 mmol) is

*Table 6.* NMR data of 1,2,3-triazoles (IV), not reported in Ref. 3 (*cf.* comments to Table 3).

| IV | $R^1$ | $R_a{}^4$ | $R^5$ |
|---|---|---|---|
| (b) | 3.96s | 2.34s | 1.31 (d, 6 H) |
| d | 3.92s | 1.7−2.2(m, 4 H), 2.4−3.0(m, 4 H) | |
| (m) | 5.49 (s, 2 H) | 2.37s | 2.98(sept., 1 H) |
| v | 7.52"s" | 1.7−2.1 (m, 4 H), 2.6−3.1(m, 4 H) | |

*Table 7.* Yields, melting points, and analyses of methyl- and benzoyl-derivatives.

| | | Yield % | M.p. °C | Formula | Analyses Found C | H | N | Calc. C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| XIV | 1 | 92 | liq. | $C_{13}H_{19}N_3O$ | 66.80 | 8.32 | 17.82 | 66.92 | 8.21 | 18.02 |
| | s | 90 | liq. | $C_{12}H_{17}N_3O$ | 65.52 | 7.93 | 19.13 | 65.72 | 7.81 | 19.16 |
| | x | 47 | 60—61 | $C_{14}H_{21}N_3O$ | 67.94 | 8.66 | 16.96 | 68.00 | 8.56 | 16.99 |
| XVI | 1 | 89 | liq. | $C_{19}H_{21}N_3O_2$ | 70.40 | 6.57 | 12.61 | 70.56 | 6.54 | 12.99 |
| | s | 100 | liq. | $C_{18}H_{19}N_3O_2$ | 69.83 | 6.27 | | 69.87 | 6.19 | |
| | x | 78 | 67—68 | $C_{20}H_{23}N_3O_2$ | 71.03 | 6.83 | 12.54 | 71.20 | 6.87 | 12.45 |

*Table 8.* NMR and IR data of methyl- and benzoyl-derivatives.

| | | NMR data Me—N | PhCO—N | $R^1$ | $R_b^4$ | $R_a^4$ | $R^5$ | IR data PhCO— | $R^5$—CO |
|---|---|---|---|---|---|---|---|---|---|
| XIV | 1 | 3.03s | | 7.31s 4.79s | 4.58q | 1.37d | 1.01t 2.43q | | 1715 |
| | s | 3.25s | | 7.0—7.7m | 4.78q | 1.48d | 1.07t 2.51q | | 1720 |
| | x | 3.18s | | 7.0—7.7m | 1.57s | | 1.08d 3.13sept. | | 1710 |
| XVI | 1 | | 7.30(s, 5 H) 7.1—7.8(m, 5 H) 4.85s | | 5.43q | 1.45d | 0.91t 2.28q | 1672 | 1720 |
| | s | | 7.41(s, 5 H) 7.2—8.0(m, 5 H) | | 5.68q | 1.60d | 1.08t 2.46q | 1675 | 1720 |
| | x | | 7.30(s, 5 H) 7.3—8.0(m, 5 H) | | 1.81s | | 1.16d 3.18sept. | 1690 | |

dissolved in 40 ml of ether, and a solution of ca. 10 mmol of diazomethane [27] in 40 ml of ether is added. The mixture is cooled to 0 °C, and two drops of boron trifluoride etherate are added. Some nitrogen evolution occurs. After ca. 30 min the mixture has become colorless. After washing with saturated $NaHCO_3$ the ether phase is evaporated. Pentane (25 ml), $Na_2SO_4$, and a little activated carbon are added, and the mixture is stirred for a few minutes. The solid materials are filtered off and the pentane solution is evaporated on a rotary evaporator. The product is usually left as a colorless oil.

The purity was checked by NMR spectroscopy. In case x purification by preparative TLC (ethyl acetate-pentane 1:4) followed by recrystallization from pentane was necessary to obtain a pure product.

*Benzoylation of 5-hydroxy-$\Delta^2$-1,2,3-triazolines (cf. Tables 7 and 8).* The triazoline (4 mmol) is dissolved in 10 ml of pyridine, and the mixture is cooled to 0 °C. Benzoyl chloride

(0.92 ml, 8 mmol) is added, and the mixture is let stand at room temperature for an hour. After cooling to 0 °C 0.2 ml of water is added, and the mixture is removed from the ice bath and left for 30 min. Ether (40 ml) is added, and after washing twice with diluted sulfuric acid (30 ml and 10 ml), once with water (10 ml), and once with saturated $NaHCO_3$ (20 ml), the ether phase is dried over $MgSO_4$ and evaporated. The products are left in an almost pure state, but for microanalysis, XVIx was recrystallized from pentane and XVIs subjected to TLC, using ethyl acetate-pentane 1:7 as eluent.

*Benzoylation of 1,4,4-trimethyl-5-isopropyl-5-hydroxy-$\Delta^2$-1,2,3-triazoline (IIf).* The benzoylation and hydrolysis of excess PhCOCl was done as in the general procedure. Instead of adding the 40 ml portion of ether, pyridine was removed on a rotary evaporator. The residue was refluxed for 2 min with 2 N $H_2SO_4$. Ether was added, and after shaking and separation, the organic phase was washed with 2 N $H_2SO_4$, water, and saturated $NaHCO_3$ and dried over

MgSO₄. Evaporation gave a residue from which 31.8 mg of XVIIf (identical with XVIIx, *vide infra*) could be crystallized from ethyl acetate-pentane. From the mother liquor additional 15.1 mg could be isolated by TLC (ethyl acetate-pentane 1:3) and crystallization from pentane. The total yield, 46.9 mg, corresponds to 49 %.

*Treatment of XIV l with hydrochloric acid.* XIV l (0.117 g) was dissolved in 0.5 ml of 3 N hydrochloric acid, and the mixture was refluxed for 3 min. After cooling, the mixture was extracted with methylene chloride (3 × 1 ml). Drying over MgSO₄ and evaporation gave 67 mg of an oil, the major part of which consisted of an equimolecular mixture of benzyl chloride and benzyl alcohol, as seen from the IR and NMR spectra.

Evaporation of the aqueous phase gave 71 mg of a colorless syrup, the hydrochloride of XV l. Benzoylation in pyridine (standing for two days) afforded 49 mg of almost pure (NMR) benzoylated XV l as a yellowish oil. It was further purified by a preparative TLC, using ethyl acetate-pentane 1:2. (Found: C 70.23; H 7.82; N 6.29. Calc. for C₁₃H₁₇NO₂: C 71.19; H 7.81; N 6.39). NMR data (CDCl₃, 100 MHz): 1.09 ("t", 3 H), 1.44 (d, 3 H), 2.1 – 3.0 (m, 2 H), 2.90 (s, 3 H), 4.0 – 5.6 (m), and 7.44 (s, 5 H).

*Treatment of XVI l with TFAA in chloroform.* XVI l (0.117 g) and TFAA (50 µl) dissolved in ethanol free chloroform (3 ml) was heated to 40 – 50 °C for 15 min. The solvent was removed in vacuum and the residue subjected to TLC (ether-pentane 2:1). Two components showed up, one of which (the slowest running) consisted of 47 mg (63 %) of XVII l. (Found: C 69.10; H 7.45; N 6.59. Calc. for C₁₂H₁₅NO₂: C 70.23; H 7.37; N 6.82). NMR data (CDCl₃, 100 MHz): 1.12 (t, 3 H), 1.46 (d, 3 H), 2.61 (dq, 2 H), 4.81 (quintet, 1 H), and 7.0 – 8.0 (m, 5 H).

*Treatment of XVIx with HCl in ether.* XVIx (0.117 g) was added to 5 ml of ether saturated with HCl, and the mixture was stirred for 30 min. A white, crystalline product separated. The mixture was cooled to 0 °C and shaken with 5 ml of water. The organic phase was dried and evaporated, yielding 73 mg (90 %) of crystalline XVIIx. After recrystallization from ethyl acetate-pentane the m.p. was 120 – 121 °C. (Found: C 71.99; H 8.34; N 6.22. Calc. for C₁₄H₁₉NO₂: C 72.07; H 8.21; N 6.00). NMR data: 1.18 (d, 6 H), 1.74 (s, 6 H), 3.24 (sept., 1 H), and 7.3 – 8.1 (m, 5 H).

The aqueous phase was added to a solution of 0.5 g of β-naphthol in 25 ml of 2 N NaOH. The separating red product was filtered off, washed with water, and dried, giving 66 mg (77 %) of red crystals with m.p. 124 – 127 °C. Recrystallization from ethanol raised the m.p. to 130 – 130.5 °C, undepressed in mixture with a sample prepared from phenyldiazonium chloride and β-naphthol.[28]

Preparation of reference compounds

*2-Bromo-2,4-dimethyl-3-pentanone.* Diisopropyl ketone (14.2 ml, 0.1 mol) was cooled in ice-water, and bromine (5.1 ml, 0.1 mol) was added dropwise and with stirring. After a short time the mixture became colorless. The product was purified by addition of 50 ml of ether, washing with saturated NaHCO₃, drying over MgSO₄, and distillation. Yield 18.4 g (95 %), b.p. 167 – 168 °C (reported [29] 166 – 168 °C). NMR data: 1.19 (d, 6 H), 1.89 (s, 6 H), and 3.49 (sept, 1 H).

*2-Anilino-2,4-dimethyl-3-pentanone* (cf. Ref. 30). 2-Bromo-2,4-dimethyl-3-pentanone (1.93 g), aniline (0.47 g), and NaHCO₃ (2.1 g) were heated in an oil bath (160 – 175 °C) for 7 h. Water (10 ml) was added, and the product was extracted with methylene chloride. Preparative TLC (ethyl acetate-pentane 1:5) and recrystallization from pentane afforded 55 % of a crystalline product, identical with VIIIx, as seen from the NMR spectrum and melting point.

*2-Methylamino-2,4-dimethyl-3-pentanone.* Methylamine (ca. 1.5 ml) was added to 2-bromo-2,4-dimethyl-3-pentanone (1.0 g) at – 76 °C in a tube. The tube was sealed and left at room temperature for 3 h. Excess of methylamine was allowed to evaporate, and the solution was acidified with hydrochloric acid. After washing with methylene chloride (3 × 2 ml) the solution was made alkaline with sodium hydroxide, and the product was extracted with methylene chloride (5 × 20 ml). Drying over MgSO₄ and evaporation yielded 0.68 g of product. NMR data: 1.06 (d, 6 H), 1.25 (s, 6 H), 2.23 (s, 3 H), and 3.16 (sept., 1 H). In addition, irrelevant signals were present at 1.08 (d), 2.39 (s), and 2.6 – 3.1 (m). The product was, however, used in the next step without further purification.

*1-Phenyl-3-methyl-3-(1,1,3-trimethyl-2-keto-butyl)triazene* (cf. Ref. 31). Aniline (93 mg, 1 mmol), dissolved in 1 ml of 3 N hydrochloric acid, was diazotized at 0 °C with 69 mg of sodium nitrite. 2-Methylamino-2,4-dimethyl-3-pentanone (143 mg) was added, and the solution was made alkaline with 2 N NaOH. The mixture was stirred at room temperature for 30 min. The oily product was extracted with methylene chloride, and the solution dried over Na₂SO₄ and evaporated, yielding 0.22 g of a reddish brown syrup. TLC (ether-pentane 1:4) afforded 147 mg (60 %) of a product, which was identical (IR, NMR, and m.p.) with XIVx.

*2-Azido-2,4-dimethyl-3-pentanone.* 2-Bromo-2,4-dimethyl-3-pentanone (3.86 g, 0.02 mol) and sodium azide (2.6 g, 0.04 mol) were dissolved with stirring in dimethyl sulfoxide (10 ml). Cooling was necessary in order to keep the temperature below 40 °C. The mixture solidified after a few minutes, but was allowed to stand at room temperature for 2 h before it was worked up. Water (10 ml) and ether (15 ml)

were added, and the ethereal phase was washed with water (2 × 10 ml), dried over MgSO$_4$, and evaporated. The azide was left in a 95 % yield as a liquid containing a trace of ether (NMR). NMR data: 1.11 (d, 6 H), 1.43 (s, 6 H), and 3.22 (sept., 1 H).

*2-Benzoylamino-2,4-dimethyl-3-pentanone.* A mixture of 2-azido-2,4-dimethyl-3-pentanone (155 mg, 1 mmol), conc. hydrochloric acid (0.3 ml), platinum oxide catalyst (5 mg), and methanol (5 ml) was hydrogenated at 1 atm. hydrogen pressure for 2 h. Platinum and methanol were removed, and the resulting α-aminoketone was treated with benzoyl chloride (1 ml) and 2 N NaOH (20 ml). Extraction with methylene chloride, drying over MgSO$_4$, evaporation, and washing with pentane gave 0.221 g (96 %) of benzoylated α-aminoketone. After recrystallization from ethyl acetate-pentane a product was obtained, which was identical with XVIIx (NMR, mixed m.p.).

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