(0.8 g.) was dissolved in 5 ml. of water and passed through a column of Amberlite IR-120 ion exchange resin. The eluate was treated with a methanolic solution of brucine of *p*H 7.5–8. After evaporation at reduced pressure the residue was recrystallized several times from methanol, giving 0.5 g. of the brucine salt. $[\alpha]_D^{25}$ −20.2° (*c*, 0.97; water). The analysis showed the salt to be the tribrucine derivative of 3-deoxy-D-gluconic acid-6-phosphate.

Anal. Calcd. for $C_{76}H_{90}O_{21}N_6P$: N, 5.83; P, 2.15. Found: N, 5.74, 5.61; P, 1.92, 1.61.

Acknowledgment. We are indebted to Mrs. Ru-Jen Lee Han for her assistance in preparing the 3-deoxy-D-ribohexose used in these experiments.

GAINESVILLE, FLA.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

The Chemistry of the Spiroaminoketal Side Chain of Solasodine and Tomatidine. I.[1] Improved Preparation of 3β-Acetoxy-5,16-pregnadien-20-one and 3β-Acetoxy-5α-pregn-16-en-20-one from Solasodine and Tomatidine.

YOSHIO SATO, NOBUO IKEKAWA,[2] AND ERICH MOSETTIG

Received September 24, 1959

The steroidal alkaloids solasodine and tomatidine have been degraded in excellent over-all yields (65–68%) to 3β-acetoxy-5,16-pregnadien-20-one and 3β-acetoxy-5α-pregn-16-en-20-one by conversion of the *O,N*-diacetates of the alkaloids into the respective pseudoacetylamino derivatives, chromic anhydride oxidation of the latter and final hydrolysis with acetic acid.

The announcement from this laboratory[3] concerning the degradation of solasodine (IA) (via VA) to 3β-acetoxy-5,16-pregnadien-20-one (IVA) has spurred several laboratories[4,5,6] to effect an increase in the yields originally obtained by us (10–20%) in this process. We wish to describe in this paper a modified and greatly improved conversion of solasodine (IA), dihydrosolasodine (IC) and tomatidine (IB) to their respective pregnenolone derivatives IVA and IVB.

When a solution of *O,N*-diacetylsolasodine[7] (IIA) in glacial acetic acid (or propionic acid) was refluxed for 15 minutes, a crystalline 3β-acetoxy-26-acetylamino-5,20(22)-furostadiene (IIIA) was obtained in a yield of 95–98%. *O,N*-Diacetyltomatidine[8] (IIB) similarly gave a 95% yield of crystalline 3β-acetoxy-26-acetylamino-5α-furost-20(22)-ene (IIIB) by this procedure. IIIA and IIIB can also be readily obtained, but not as pure and in as good yields, by treating a solution of IIA and IIB respectively in acetic acid with mineral acids (perchloric or hydrochloric) at room temperature.[9] IIIA has previously been obtained by chromatography on alumina of the crude reaction mixture resulting from the treatment of solasodine with acetic anhydride.[10] The 3-hydroxy compound of IIIB has likewise been obtained by the alkaline hydrolysis of the so-called unsaturated triacetyltomatidine (VB).[11]

By chromic acid oxidation of the pseudo compounds IIIA and IIIB in aqueous acetic acid (80%) and subsequent hydrolysis of the acyloxy side chain with acetic acid according to the method of Cameron *et al.*[12] the respective pregnenolone acetates IVA and IVB were obtained in high yields. We have found that optimal results were obtained in the oxidation when two molar equivalents of chromium trioxide were used. Although these products are crystalline and can be readily purified by recrystallization, it has been found expedient to resort to chromatography at this stage. The yields of IVA and IVB (from IIA and IIB) ranged from about 75–80%. In a continuous operation, *i.e.* without the isolation and purification of IIA and IIIA, solasodine (IA) gave 65% of the pregnenolone derivative IVA. Similarly, tomatidine

(1) A preliminary account of this work was published in *J. Org. Chem.*, **24**, 893 (1959).

(2) Visiting Scientist, National Institutes of Health.

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(9) The chemistry and structure proof of the byproduct obtained in this reaction will be discussed in a forthcoming publication of this series.

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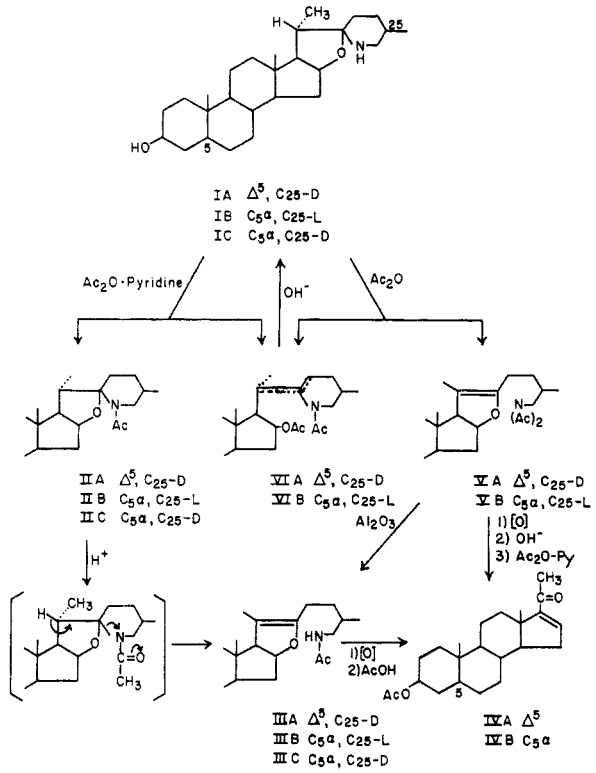

Compounds represented by partial formulas II, III, V, and VI possess a 3β-acetoxy function

(IB) yielded 68% of IVB. Dihydrosolasodine[13] (IC) also gave allopregnenolone acetate, IVB, in comparable yields via IIC and IIIC. As the degradation of these steroidal alkaloids starts from the corresponding *O,N*-diacetyl derivatives, it is of obvious importance to secure them in maximum yields. It is recognized[14] that considerable difference exists between these alkaloids in their behavior toward acetylation. Tomatidine(IB) can be readily acetylated in the conventional manner (acetic anhydride-pyridine, room temperature) to give in good yields the desired diacetate IIB, whereas solasodine (IA) under these conditions is not completely acetylated. Under more vigorous conditions normal diacetylation is accompanied by varying amounts of byproduct formation, VIA.[15] For example, if acetylation is conducted under the conditions of Briggs and O'Shea[7] (eight moles acetic anhydride-pyridine, two hours boiling) and the resulting product chromatographed, a mixture of VIA is obtained in about 20% yield in addition to the normal *O,N*-diacetyl derivative IIA. After attempting acetylation by various methods (acetic anhydride-pyridine-sodium acetate-reflux; acetic anhydride-pyridine-triethylamine-reflux; ketene), we found the use of 3.8 mole equivalents of acetic anhydride in pyridine (one hour boiling) to be the most satisfactory resulting in a minimum formation of VIA. 5,6-Dihydrosolasodine (IC) was found to behave in the same way towards acetylation as solasodine. It is of interest to note that VIA was formed almost to the extent of 50% when solasodine (IA) was refluxed with acetic anhydride for several hours.[10] The same treatment of tomatidine (IB)[16] yields VIB to a much lesser extent (20–25%). As oxidation[17] of VIA or VIB does not give the desired pregnenolones, the poor yield of the pregnadiene derivative IVA (in contrast to the fairly good yield of IVB) by the procedure formerly reported by us[10] is readily explained. As 5,6-dihydrosolasodine (IC) behaves more like solasodine than tomatidine, it is most probable that the difference in configuration of solasodine and tomatidine at C_{25}[18,19] is responsible for their behavior towards acetylation.

A salient feature of the byproducts VIA and VIB is that they can be readily reconverted into the corresponding original alkaloids IA and IB by treatment with alcoholic alkali.

The above series of conversions demonstrate that these steroidal alkaloids, and particularly solasodine, bear promise of serving as commercial starting material in the synthesis of steroidal hormones.

EXPERIMENTAL[20]

Acetic anhydride treatment of solasodine (IA) *to give 26-acetylamino-furosta-5,20(22)dien-3β-ol acetate* (IIIA) *and amorphous mixture* VIA. A solution of 824 mg. of solasodine in 15 ml. of acetic anhydride was refluxed for 3 hr. The acetic anhydride was removed *in vacuo* and the residue dissolved in benzene and placed on an alumina column to stand overnight. Elution with benzene-ether (1:1) the following morning gave 546 mg (51%) of an amorphous substance (VIA), m.p. 98–102°, $[\alpha]_D^{20}$ −3° ($CHCl_3$); $\lambda_{max}^{CHCl_3}$ 5.78 (acetoxy), 5.98, 6.07 μ; λ_{max}^{EtOH} 236 mμ (log ε 3.95).

Anal. Calcd. for $C_{33}H_{49}O_5N$: C, 73.43; H, 9.15; CH_3CO, 23.9. Found: C, 73.31; H, 9.07; CH_3CO, 24.3.

Elution with 0.5% methanol in ether yielded 398 mg. (40%) of the pseudo derivative, IIIA, which crystallized from acetone-hexane, m.p. 135–138°, identical in all respects with the substance obtained from the acetic acid catalyzed rearrangement of IIA. A small amount of a third component m.p. 175–178° (from acetone-hexane) was eluted with 2% methanol in ether; its structure will be discussed in a forthcoming paper. There was no substantial difference in the composition and yield when the reaction time of acetic anhy-

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(15) The chemistry and proof of structure of this mixture will be published in a forthcoming publication.

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(19) Schreiber (14) also proposes a C_{22} isomerism for dihydrosolasodine and tomatidine but the evidence is meager and inconclusive.

(20) Melting points were taken on the Kofler block and are uncorrected. Microanalyses were performed by the Analytical Service Laboratory under the direction of Dr. William C. Alford. Woelm alumina, grade 1, was used in the chromatography.

dride with solasodine was prolonged to 9 hr. Solasodine was also refluxed with propionic anhydride but the yields of the product as indicated by chromatography were not as good.

Acetic anhydride treatment of tomatidine (IIB) *to give 26-aminodiacetyl-5α-furost-20(22)en-3β-ol acetate* (VB), *26-aminoacetyl-5α-furost-20(22)en-3β-ol acetate* (IIIB) *and amorphous mixture* VIB. Tomatidine (378 mg.) was refluxed with 10 ml. of acetic anhydride for 3 hr. After the reaction mixture was worked up in the manner previously reported[16] 195 mg. (40%) of crude VB was recovered. The mother liquor was evaporated to dryness and the residue subjected to alumina chromatography. Upon elution with benzene-ether (1:1) 115 mg. (23%) of an amorphous substance, m.p. 97–102°, VIB, $[\alpha]_D^{20}$ +92.5° ($CHCl_3$), λ_{max}^{EtOH} 236 mμ (log ε 3.92), $\lambda_{max}^{CHCl_3}$ 5.78 μ (acetoxy), 5.99, 6.08 μ was obtained.

Anal. Calcd. for $C_{33}H_{51}O_5N$: C, 73.16; H, 9.49; CH_3CO, 23.9. Found: C, 72.90; H, 9.31; CH_3CO, 25.5.

Elution with 0.5% methanol in ether yielded 145 mg. (32%) of IIIB, which after crystallization from acetone-hexane melted at 128–132°. This substance agreed in properties with IIIB obtained from the acetic acid catalyzed rearrangement of IIB.

Acetylation of solasodine to give IIA and VIA. (a) (8 mole equiv. of acetic anhydride). A solution of solasodine (520 mg.) 5 ml. of pyridine and 1 ml. of acetic anhydride was refluxed for 1 hr. and was poured on ice, followed by addition of aqueous ammonia and sodium chloride. After 1 hr. the product was collected and chromatographed on alumina (Grade 1). The diacetate (IIA) was eluted with benzene-ether (1:1), yield 410 mg. (65%), m.p. 164–166°.

Fractions eluted with ether-methanol (1%) gave 228 mg. of amorphous compound, which was rechromatographed on alumina (Grade II). Elution in this chromatography with benzene-ether (3:1) gave 136 mg. (20%) of VIA, identical in infrared spectrum with VIA obtained from the acetic anhydride treatment of solasodine. Further elution with ether-methanol (1%) gave 6% of an unresolved mixture.

(b) (3.8 mole equiv. of acetic anhydride) A mixture of 520 mg. of solasodine, 5 cc. of pyridine, and 0.46 ml. of acetic anhydride was refluxed for 1 hr. and the reaction mixture worked up as described above. Purification by chromatography on alumina or recrystallization from aqueous methanol gave 575 mg. (92%) of diacetate IIA. A second crop raised the yield to 95%.

(c) The yields after acetylation of solasodine under various conditions are tabulated below:

Acetic Anhydride-Pyridine	Time	Diacetate Yield (after chromatography)
2.2 mole equiv.	2 hr. (reflux)	55–60%
2.7 mole equiv.	2 hr. (reflux)	75%
3.5 mole equiv. plus sodium acetate (3 mole equiv.)	1.7 hr. (reflux)	85%
4 mole equiv. plus triethylamine (*ca.* 4 mole equiv.)	1 hr. (reflux)	85%
10 mole equiv.	15 hr. (room temp.)	30–40%
6 mole equiv.	15 hr. (5°)	mostly 3-acetate

With excess ketene an unpromising looking mass was obtained which was not investigated further.

Acetylation of Tomatidine to give IIB. A mixture of tomatidine (505 mg), 8 ml. of pyridine and 2 ml. (*ca.* 8 mole equiv.) of acetic anhydride was allowed to stand overnight and poured on ice and aqueous ammonia. The precipitated diacetate was recrystallized from petroleum ether-ether, fine needles, m.p. 184–188°, yield 585 mg. (96%). After recrystallization, the melting point rose to 190–192°.

Acetylation of Dihydrosolasodine to give IIC. A solution of dihydrosolasodine (100 mg.) and 0.1 cc. (*ca.* 4 mole equiv.) of acetic anhydride in 2 ml. of pyridine was refluxed for 1 hr. and poured into ice water. The product was collected, dried and chromatographed over alumina. The fraction eluted with ether gave 109 mg. (92%) of diacetate, m.p. 180–183°.[21]

A solution of dihydrosolasodine (100 mg.) and 0.75 cc. (*ca.* 30 mole) of acetic anhydride in 2 ml. of pyridine was allowed to stand for 15 hr. The product was chromatographed over alumina. The fraction eluted with ether gave 70 mg. (58%) of impure diacetate, (m.p. 155–170°) as revealed by its infrared spectrum.

26-Acetylamino-5,20(22)-furostadiene-3β-ol acetate (IIIA). (a) To boiling acetic acid (10 ml.), 500 mg. of solasodine diacetate (IIA) was added in small portions and refluxed further for 15 min. The solvent was evaporated *in vacuo* and the crystalline residue was recrystallized from acetone-hexane, m.p. 135–138°, $[\alpha]_D^{20}$ −23° ($CHCl_3$), $\lambda_{max}^{CHCl_3}$ 2.90, 2.98 μ (N—H); 5.78 μ (3-acetoxy); 5.89 μ (vinyl ether, nujol); 5.98, 6.60 μ (N—H acetyl). The product may be chromatographed on an alumina column and eluted with 0.5% methanol in ether. The yields range from 95–98%.

Anal. Calcd. for $C_{31}H_{47}O_4N$: C, 74.81; H, 9.52. Found: C, 75.09; H, 9.36.

When propionic acid was used in place of acetic acid, the result was about the same.

(b) A solution of 235 mg. of IIA, 3 ml. of acetic acid, and 0.03 ml. of perchloric acid (60%) was allowed to stand at room temperature for 10 min., was poured on ice, and was partially neutralized with aqueous ammonia. The product was collected and dissolved in ether. After drying, the ether was evaporated and the residue was chromatographed on alumina.

From the fraction eluted with ether-methanol (0.5%) 171 mg. (73%) of pseudo compound (IIIA), m.p. 135–138° was obtained. A subsequent fraction eluted with ether-methanol (5%) gave 52 mg. (23%) of a crystalline hydroxyl derivative[9] which melted rather unsharply at 144–152°.

When hydrochloric acid (36%) was substituted for perchloric acid, the results were approximately the same.

26-Aminoacetyl-5α-25L-furost-20(22)-en-3β-ol acetate (IIIB). Tomatidine diacetate (IIB) (322 mg.) was converted into IIIB, m.p. 125–129°, 309 mg. (96%) in the same manner [method (a)] described above for IIIA. A sample recrystallized from acetone-hexane melted at 128–132°, $[\alpha]_D^{20}$ +1.5° ($CHCl_3$), $\lambda_{max}^{CHCl_3}$ 2.89, 2.97 μ (N—H); 5.78 μ (3-acetoxy); 5.89 μ (vinyl ether, nujol); 5.99, 6.59 μ (N—H-acetyl).

Anal. Calcd. for $C_{31}H_{49}O_4N$: C, 74.51; H, 9.88. Found: C, 74.66; H, 10.02.

26-Acetylamino-5α-25D-furost-20(22)-en-3β-ol acetate (IIIC).

IIIC was prepared in the manner [method (a)] of IIIA; IIC (120 mg.) yielded 111 mg. (93%) of IIIC, after alumina chromatography and elution with ether-methanol (0.5%), m.p. 78–80°, $[\alpha]_D^{20}$ +22° ($CHCl_3$), $\lambda_{max}^{CHCl_3}$ 2.90, 2.98 μ (N—H), 5.79 μ (3-acetoxy), 5.99, 6.60 μ (N—H-acetyl).

Anal. Calcd. for $C_{31}H_{49}O_4N$: C, 74.51; H, 9.88. Found: C, 74.53; H, 10.09.

Oxidation of IIIA to 3β-acetoxypregna-5,16-dien-20-one (IVA). A solution of chromic anhydride (110 mg., 2 mole equiv. in 8 ml. of 80% aqueous acetic acid) was added dropwise over a period of 15 min. to a stirred solution of IIIA (280 mg.) in 10 ml. of acetic acid while cooling (15°). After the addition of the oxidant, the solution was stirred for 1 hr. at room temperature. Water (*ca.* 50 ml.) and a small amount of sodium sulfite were added. The mixture was saturated with sodium chloride and extracted with ether thoroughly. The combined ether extractions were dried over anhydrous sodium sulfate and the solvent (ether) was removed. The residue was dissolved in 25 ml. of acetic acid and refluxed for 2 hr. After removal of the acetic acid and

(21) Reported (7) m.p. 186–187°.

dilution with water, it was neutralized with sodium bicarbonate and extracted with ether. The ether layer was washed with sodium bicarbonate solution and water, and dried over anhydrous sodium sulfate. The residue (215 mg.) after removal of the solvent was recrystallized from methanol-water or chromatographed over alumina (ether eluate) and gave 152 mg. (76%) of IVA, m.p. 169–173°, analytical sample, m.p. 173–175.5°, $[\alpha]_D^{20}$ −35° ($CHCl_3$), λ_{max}^{EtOH} 239 mμ (log ε 4.0), identical in all respects with an authentic specimen.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.45; H, 9.11.

In a continuous operation from solasodine (IA) (1 g.) using 3.8 mole equiv. of acetic anhydride for the acetylation and without purification or isolation of the intermediates, an over-all yield of 65% of IVA, m.p. 169–173° was obtained.

A small amount of the lactone and a second component presumably the 3,5-diene were often detected by infrared spectra in these oxidations.

Oxidation of IIIB to 3β-acetoxy-5α-pregn-16-en-20-one (IVB). A solution of chromic anhydride (146 mg., 2 mole equiv.) in 10 ml. of 80% aqueous acetic acid was added over a period of 15 min. to a stirred solution of 365 mg. of IIIB in 16 ml. of acetic acid while cooling (10–20°). After stirring for 1 hr. at room temperature, the reaction mixture was worked up as described above for IVA and 285 mg. of oxidation product was obtained. Purification of the crude product by recrystallization from methanol-water or chromatography on alumina gave 206 mg. (79%) of IVB, m.p. 163–166°, analytical sample m.p. 165–167°, $[\alpha]_D^{20}$ +42° ($CHCl_3$), λ_{max}^{EtOH} 239 mμ (log ε 3.98). It agreed in all properties with an authentic sample.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.32; H, 9.58.

In a continuous operation from tomatidine (IB), analogous to solasodine, an over-all yield of 68% of IVB was obtained.

Oxidation of IIIC *to 3β-acetoxy-5α-pregn-16-en-20-one* (IVB). A solution of chromic anhydride (90 mg., 2 mole equiv.) in 7 ml. of 80% aqueous acetic acid was added over a period of 15 min. to a stirred solution of IIIC (230 mg.) in 8 ml. of acetic acid while cooling. After stirring for 1 hr. the reaction mixture was worked up in a manner similar to that described above for IVA. The crude product (188 mg.) was chromatographed over alumina; the fraction eluted with ether gave 123 mg. (75%) of IVB, m.p. 163–166°, identical in all respects with an authentic specimen.

Solasodine (IA) *from* VIA. A solution of 100 mg. of VIA in 20 cc. of 10% methanolic potassium hydroxide was refluxed for 12 hr. After partial concentration of the volume and addition of water, the product was collected and dried. Upon crystallization from aqueous methanol or chromatography over alumina (Grade II eluted with 2% methanol in ether), 61 mg. (80%) of IA, m.p. 199–202°, was obtained, identical in every respect with an authentic specimen of solasodine.

Tomatidine (*IB*) *from VIB.* Tomatidine was obtained from VIB in the same manner as described above for solasodine.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

The Chemistry of the Spiroaminoketal Side Chain of Solasodine and Tomatidine. II.[1] Chemistry of 3β,16β-Diacetoxy-20-(2′-Δ$^{2'}$-*N*-acetyl-5′-methyltetrahydropyridyl)-5-pregnene

YOSHIO SATO AND NOBUO IKEKAWA[2]

Received September 24, 1959

The chemistry and the manifold interrelationship of the acetylated tetrahydropyridyl pregnenes and the diacetylaminofurostadiene derivative obtained in the treatment of solasodine with acetic anhydride are discussed.

The reaction of solasodine (I) with acetic anhydride[3] (three hours boiling) leads to the formation of a gummy resinous mass which is presumably a mixture of 26-aminodiacetyl-5,20(22)-furostadien-3β-ol acetate[4] (III), Δ$^{22(23)}$ tetrahydropyridylpregnene derivative IIA and the probable isomeric Δ$^{20(22)}$ piperidylpregnene derivative IIB. Upon chromatography[3] of this mixture on alumina, III is readily deacetylated and emerges from the column as 26-acetylamino-5,20(22)-furostadien-3β-ol acetate (VIa). It can be reconverted to the original hitherto unisolated crystalline aminodiacetyl derivative III by treatment with acetic anhydride and pyridine. The degradation of VIa to 3β-acetoxy-5,16-pregnadien-20-one has been described in the foregoing paper.[1] Compounds IIA and IIB, which are eluted from the column as an amorphous mixture, are assigned their structures from considerations of spectroscopic and chemical data. The mixture exhibits an ultraviolet absorption band at 236 mμ (log ε, 3.95) consistent with the assignment of an α,β-unsaturated acetylamino function.[5,6] The infrared spectrum reveals the

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(2) Visiting Scientist, National Institutes of Health.

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(4) *Cf.* Y. Sato, A. Katz, and E. Mosettig, *J. Am. Chem. Soc.*, **74**, 538 (1952). Compound III has never been directly isolated from the reaction mixture. It is assumed that the reaction proceeds in the same manner as with tomatidine where the corresponding 26-aminodiacetyl derivative can be directly crystallized from the reaction mixture. The chemistry of these related tomatidine derivatives will be discussed in a forthcoming publication.

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