1 H, HCO), 7.50 and 7.37 (B part of AB, 2 H, arom), 7.03 and 6.90 (A part of AB, 2 H, arom), 7.00 (s, 5 H, phenyl), 6.03 (d, J = 9 Hz, 1 H, NH), 4.60 (d of d, J = 9 Hz, J = 7 Hz, 1 H, HCPh), 2.83-2.40 (m, 1 H, HCEt), 2.40 (s, 3 H, CH_3SO_2), 1.97-1.47 (m, 2 H, CH_2), 0.87 (t, 3 H, J = 7 Hz, CH_3). Anal. Calcd for $C_{18}H_{21}NSO_3$: C, 65.23; H, 6.39; N, 4.23. Found: C, 65.11; H, 6.17; N, 4.22.

The aldehyde **17dc** (threo) was obtained as an oil from the azetidine **16dc** cis,trans. Because the azetidine could not be obtained completely pure, the aldehyde was contaminated with about 5% of the erythro aldehyde. The mass spectrum showed the same peaks as for the erythro aldehyde. Typical peaks in the ^{1}H NMR are δ 9.57 (d, J = 4 Hz, 1 H, HC=O), 4.57 (d, J = 8 Hz, 1 H, HCPh after addition of p-toluenesulfonic acid).

C(2)-Functionalized Tryptophans from 3-Acetoxyindoles and Their Possible Implication in Indole Alkaloid Biosynthesis†

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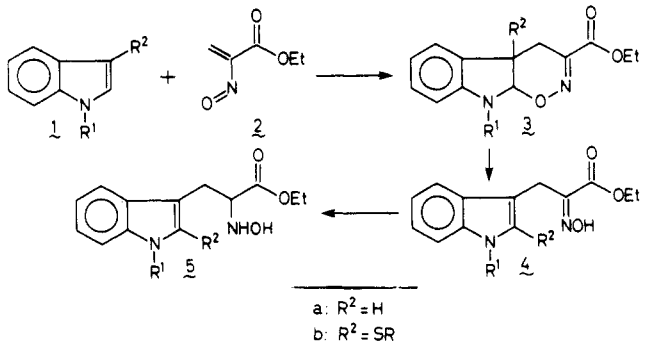
The acetoxyindoles **10** and **11** are efficiently converted (85-95%) into the dihydro-1,2-oxazines **13** and **14**, respectively, by reaction with the transient nitroso olefin **2**, prepared in situ from ethyl α-(hydroxyimino)-β-bromopropanoate by base treatment. The cycloadducts **13** and **14** react efficiently with thiols or a hydride donor to yield (60-90%) the 2-substituted tryptophan derivatives **9a-f**. Selective reduction of the oxime function of the 2-(*S*-cysteinyl)tryptophan derivative **9d** afforded **19**, a derivative of tryptathionine. The sulfonium salt **22b** derived from 2-(ethylthio)tryptophan derivative **9b** was shown to undergo a thio-Claisen rearrangement to yield **26**. This reaction supports Bycroft's proposal involving a thio-Claisen rearrangement in indole alkaloid biosynthesis.

Introduction

The biogenetic relationship between tryptophan and α-substituted, α,β-disubstituted, or α,β-dehydro tryptophans has been suggested to proceed via *N*-hydroxytryptophan derivatives.[1] This postulate is supported by the biosynthetic pathway to glucosinolates derived from tryptophan (e.g., glucobrassicins[2a]) which proceeds via *N*-hydroxytryptophan[2b,c] and by the recent isolation of astechrome[3] and the eudistomins,[4] natural products having *N*-hydroxytryptophan—or a derivative thereof—as a characteristic structural element. We have shown, moreover, that *N*-hydroxytryptophan deserves attention not only as a biosynthetic precursor, but also as a synthon for natural products featuring tryptophan derivatives.[1,5]

One of the approaches we explored successfully for the synthesis of *N*-hydroxytryptophan **5** and related compounds starts with the cycloaddition of the nitroso olefin **2** to the C(2)-C(3) double bond of indol (**1a**) to yield **3a** (Scheme I). Base-catalyzed ring opening and rearomatization afforded **4a**.[1] As part of a further exploration of this reaction we observed recently[6] that the cycloaddition of **2** to 3-(alkylthio)indoles **1b** gave **4b** in which the alkylthio group had migrated from C(3) to C(2). This rearrangement occurs with good yields under mild conditions (room temperature, CH_2Cl_2, Na_2CO_3) and is rationalized as represented in Scheme II. The indolenine **6b**, being in equilibrium with **3b**, might form the episulfonium ion **7** which yields **4b** by rearomatization. The cycloadducts **3a** and **3b** appeared to be unstable intermediates, which escaped isolation. We became intrigued by the potential usefulness of a stable derivative of cycloadduct **3**. We reasoned that if substituent R^2 has a low migratory aptitude, **3** might be an isolable compound that might react with external nucleophiles as depicted in Scheme II, sequence **3** → **6** → **8** → **9**. Here we report that this approach

Scheme I



is viable. Cycloadduct **3** can be isolated indeed when R^2 is an acetoxy group. Treatment with nucleophiles yields **9**, a reaction for which we propose **8** as an intermediate.

Results

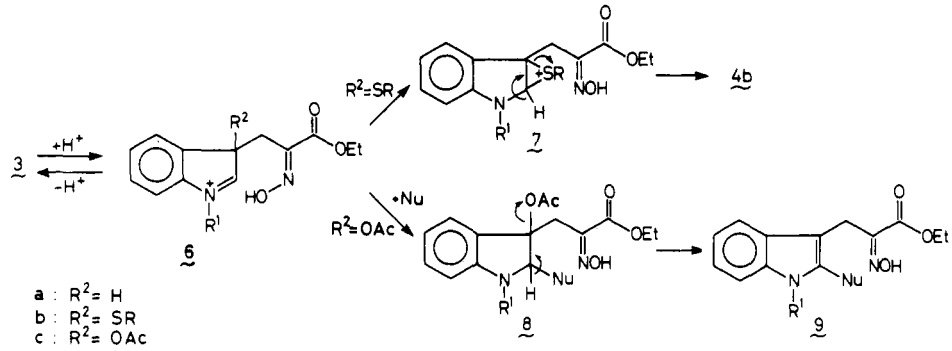
The 3-acetoxyindoles **10-12** (Scheme III) were prepared according to literature procedures.[7] Reaction of **11** with **2**—prepared in situ by treatment of ethyl α-(hydroxyimino-β-bromopropanoate[1,8] with Na_2CO_3—afforded regio- and stereospecifically the desired dihydro-1,2-oxazino-

† Presented in part at the Eleventh International Symposium on the Organic Chemistry of Sulfur, Lindau, FRG., September 10-14, 1984; see *Phosphorus Sulfur* **1985**, *24*, 129.

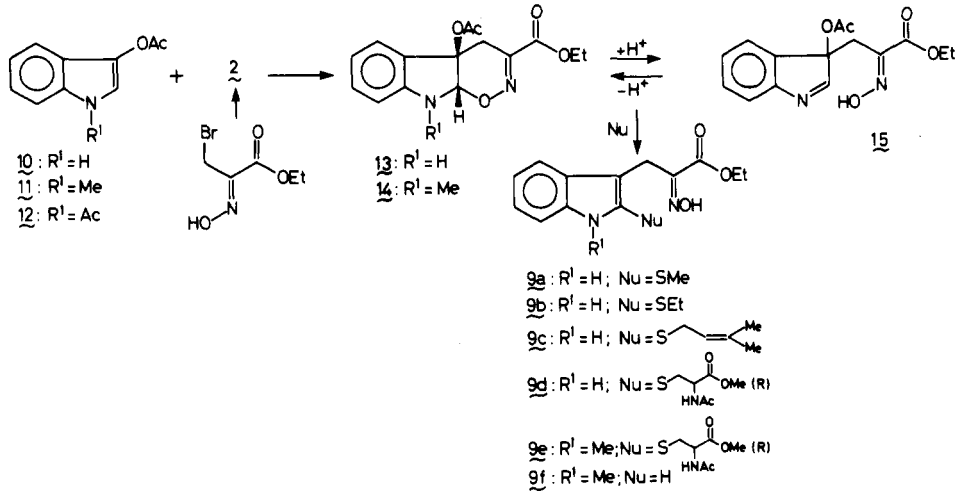
(1) Ottenheijm, H. C. J.; Plate, R.; Noordik, J. H.; Herscheid, J. D. M. *J. Org. Chem.* **1982**, *47*, 2147.
(2) (a) Gmelin, R.; Virtanen, A. I. *Acta Chem. Scand.* **1962**, *16*, 1378. (b) Møller, B. L. In *Cyanide in Biology*; Vennesland, B., Conn, E. E., Knowles, G. J., Eds.; Academic: London, 1981, p 197 and references cited therein. (c) Mahadevan, S. *Ann. Rev. Plant Physiol.* **1973**, *24*, 69.
(3) Arai, K.; Sato, S.; Shimizu, K.; Nitta, K.; Yamamoto, Y. *Chem. Pharm. Bull.* **1981** *29*, 1510.
(4) Rinehart, K. L.; Kobayashi, J.; Harbow, G. C.; Hughes, R. G.; Mizsak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 1524.
(5) Plate, R.; Hermkens, P. H. H.; Ottenheijm, H. C. J. *J. Org. Chem.* **1986**, *51*, 309.
(6) Plate, R.; Ottenheijm, H. C. J.; Nivard, R. J. F. *J. Org. Chem.* **1984**, *49*, 540.
(7) Ettinger, L.; Friedlander. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 2075. Vorlaender, D.; Mumme, E. Ibid. **1902**, *35*, 1699.
(8) The employment of this heterodiene **2** in cycloaddition reactions has been described for the first time by Gilchrist, T. L.; Longham, D. A.; Roberts, T. G. *J. Chem. Soc., Chem. Commun.* **1979**, 1089.

0022-3263/87/1952-0370$01.50/0

Scheme II

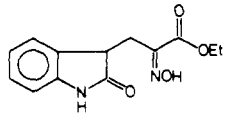


Scheme III



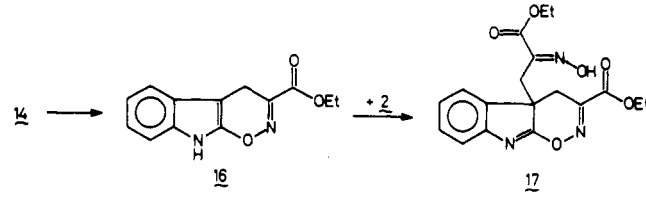
[5,6-*b*]indole derivative **14** in 90% yield. Cycloaddition of **10** with **2** gave quantitatively a mixture of **13** (85%) and **15** (15%). *N*-Acetyl-3-acetoxyindole (**12**) did not yield the cycloadduct; treatment with a molar excess of **2** for several days at elevated temperature led only to decomposition of **2**. This failure can be attributed to the lowered electron density of the C(2)–C(3) double bond of **12**. The adducts **13** and **14** were isolable compounds which showed no tendency to rearrangement as observed for **3b**. Interestingly, compound **13** could be converted partially into **15** by mild acid treatment, e. g., with silica gel. Treatment with stronger acids (e.g., CF_3COOH) gave decomposition products and **17**. The formation of **17** may be ascribed to elimination of acetic acid to yield **16** and reaction of the latter with **2** formed by a retroaddition reaction of **13**[9] (Scheme IV).

Exposure of freshly prepared **13** or **14** to thiols, viz., methanethiol, ethanethiol, 3-methyl-2-butenethiol, and *N*-acetyl-L-cysteine methyl ester, gave the corresponding 2-(alkylthio)tryptophan derivatives **9a–e**, respectively. Yields—ranging from 60 to 74%—were highest when **14** and the lower thiols were employed. Although this reaction requires an acidic medium (CF_3COOH in CH_2Cl_2 or HCl in dioxane), formation of **17** was not observed now. Occasionally, the oxindole **18** was isolated as a byproduct in



18

Scheme IV



the reaction of **13** with *N*-acetylcysteine methyl ester. Its formation during this reaction, which was rather sluggish, may be ascribed either to solvolysis[10] of **9d**, a possible C(3)–C(2) migration of the acetoxy group[11] in **15**, or to a β-elimination of the cysteinyl moiety followed by solvolysis of the resulting thioindole under the workup conditions used ($NaHCO_3$). We consider the first explanation as well as a C(3)–C(2) migration of the acetoxy group less probable since **18** could not be detected during the formation of **9a,c,e,f** (Scheme III) and **17** (Scheme IV).

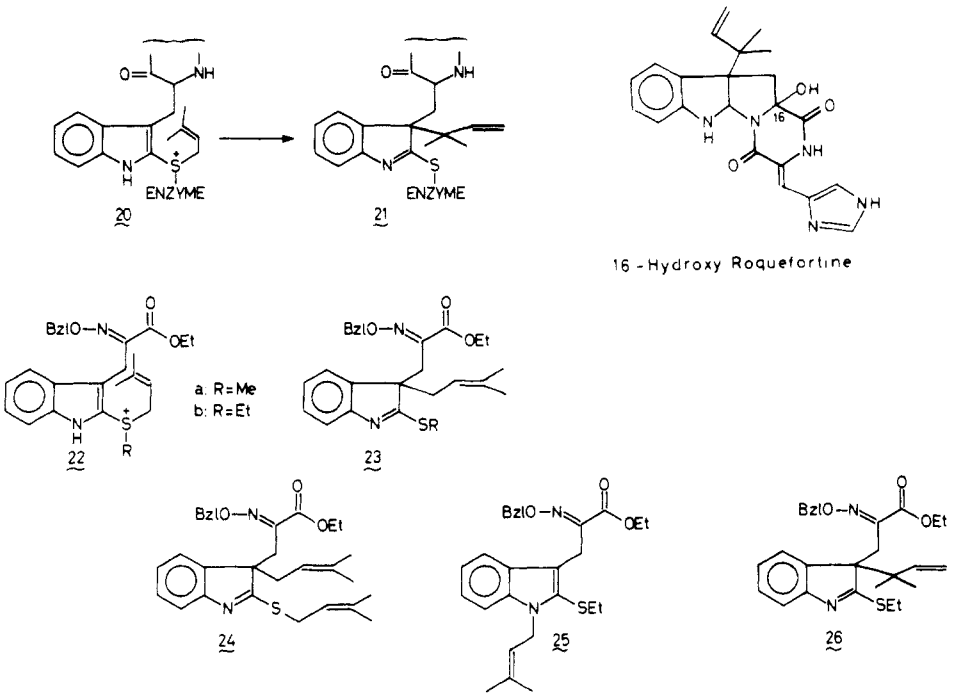
Reactions of **13** or **14** with other nucleophiles were studied only superficially. Treatment of **14** with a hydride donor ($Me_3H{\cdot}BH_3$) gave **9f** in 91% yield. The reaction with alcohols (ethanol, isopentanol) and amines (*n*-butylamine) has so far been unsuccessful. Instead of substitution, decomposition of **13** and formation of **17** were observed. We conclude tentatively that the dihydro-1,2-oxazine ring of **13** and **14** is only susceptible to nucleophilic attack when soft nucleophiles are employed.

(9) Davies, D. E.; Gilchrist, T. C. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1479.

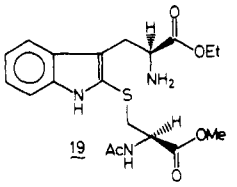
(10) Wieland, Th.; Weiberg, O.; Dilger, W. *Justus Liebigs Ann. Chem.* **1955**, *592*, 69.

(11) Sundberg, R. J. In *The Chemistry of Indoles*; Academic: New York, 1970; p 316.

Scheme V



Compounds **9c** and **9d** were further studied in relation to our studies on the biomimetic synthesis of indole alkaloids. Compound **9d** was converted into **19**, an N,O-



protected derivative of tryptathionine. As described previously,[12] treatment with aluminum amalgam gave (70% yield) a mixture of two diastereomers out of which **19** was isolated by HPLC. This 2-(cysteinyl)tryptophan derivative is a characteristic constituent of phalloin and related toxic peptides from the mushroom *Amanita phalloides*.[13] Subsequently, we studied whether a sulfonium cation of the compound **9c** might undergo a thio-Claisen rearrangement. Bycroft has postulated[14] that enzyme-bound C(2)-sulfonium salts of tryptophans (e.g., **20**) might be intermediates in the biosynthesis of natural products from moulds and marine sources[15] featuring a 3-(1,1-dimethyl-2-propenyl)indolenine moiety, **21** (Scheme V) (e.g., 16-hydroxyroquefortine[15b]). The conversion of **20** into **21** is an example of a thio-Claisen rearrangement.[16] We reasoned that **9c** is suited to test Bycroft's postulate, which at the outset of our study had only been supported by approaches using C(3)-unsubstituted indoles or skatole derivatives.[14]

We found that **9c** does not undergo a spontaneous or acid-induced thio-Claisen rearrangement. The methylsulfonium cation **22a**, prepared by treatment of **9c** with benzyl bromide and a base (76% yield) and subsequent reaction with MeI/HgI_2[17] rearranged spontaneously into **23a** (25%) and **24** (13%) as major products. However, the product of a thio-Claisen rearrangement was not detected in this reaction. The formation of **23a** and **24** can be rationalized by a reaction between **22a** and its precursor, i.e., the corresponding sulfide. We consider this intermolecular transfer of the dimethylallyl group more likely than an intramolecular transfer in **22a** involving a high-energy, four-membered transition state.

Because of this failure, a slightly modified approach was studied. The ethylsulfonium cation **22b** was prepared by reaction of **9b** with benzyl bromide and a base (74% yield) and subsequent treatment with dimethylallyl bromide in acetone. From the resulting reaction mixture compounds **25** (48%) and **23b** (25%) could be isolated as the major products, but, moreover, compound **26**, the product of the desired thio-Claisen rearrangement, was also formed, though in low yield (16%). The ^{1}H-NMR spectrum of **26** indicated the presence of a 1,1-dimethyl-2-propenyl group at the C(3)-position of the indolenine moiety. The chemical shift values are comparable with those observed in the spectra of natural products[15] and are nearly identical with those observed in the spectra of synthetic compounds[18] closely related to **26**. The conversion **22b** → **26** provides

(12) Plate, R.; Nivard, R. J. F.; Ottenheijm, H. C. J. *Tetrahedron* **1986**, *42*, 4503.

(13) For a recent review, see: Wieland, *Th. Int. J. Peptide Protein Res.* **1983**, *22*, 257.

(14) Bycroft, B. W.; Landon, W. *J. Chem. Soc. Chem. Commun.* **1970**, 967. Later on this postulate was strengthened by the observation that the indole C(2) proton is lost during the biogenesis of indole derivatives having this moiety (**21**), e.g., roquefortine.[15a]

(15) For example: (a) Roquefortine, see: Scott, P. M.; Merrien, M. A.; Polonsky, J. *Experientia* **1976**, *32*, 140. (b) 16-Hydroxyroquefortine, see: Steyn, P. S.; Vleggaar, R. *J. Chem. Soc. Chem. Commun.* **1983**, 560. (c) LL-S490β, see: Ellestadt, G. A., Mirando, P.; Kunstmann, M. P. *J. Org. Chem.* **1973**, *38*, 4204. Oxaline and neoxaline, see: Konda, Y.; Onda, M.; Hirano, A.; Omura, S. *Chem. Pharm. Bull.* **1980**, *28*, 2987. Aszonalenin, see: Kimura, Y.; Hamasaki, T.; Nakajima, H.; Isogai, A. *Tetrahedron Lett.* **1982**, *23*, 225. Flustramine A and B, see: Carle, J. S.; Christophersen, C. *J. Am. Chem. Soc.* **1979**, *101*, 4012. Flustramine C, see: Carle, J. S.; Christopherson, C. *J. Org. Chem.* **1981**, *46*, 3441. Amauramine, see: Takase, S.; Kawai, Y.; Uchida, I.; Tanaka, H.; Aoki, H. *Tetrahedron Lett.* **1984**, 25, 4673; Nigrifortine, see: Laws, I.; Mantle, P. G. *Phytochemistry* **1985**, *24*, 1395.

(16) During the preparation of this manuscript a smooth thio-Claisen rearrangement via sulfoxides has been reported. Block, E.; Ahmad, S. *J. Am. Chem. Soc.* **1985**, *107*, 6731.

(17) This method has been employed for alkylation of aryl sulfides. Van der Veen, J. *Recl. Trav. Chim. Pays Bas* **1965**, 84, 540.

(18) (a) Takase, S.; Itoh, Y.; Uchida, I.; Tanaka, H.; Aoki, H. *Tetrahedron Lett.* **1985**, *26*, 847. (b) Takase, S.; Uchida, I.; Tanaka, H.; Aoki, H. *Heterocycles* **1984**, *22*, 2491.

support for Bycroft's postulate[14] and may be seen as a chemical analogy for the enzymatic mode of introduction of the dimethylallyl group in several classes of indole alkaloids. We made no attempts to improve this reaction or to study it in more detail, since during the course of the research under consideration a related reaction utilizing the thio-Claisen rearrangement in question has been reported.[18]

Discussion

The procedures described provide a new and simple approach to 2-(alkylthio)tryptophan derivatives **9a–e**. The oxime function of these products can be reduced selectively to either the corresponding *N*-hydroxyamino[19] or unsubstituted amino group (vide supra). The resulting class of compounds, 2-(alkylthio)tryptophan derivatives, was previously obtained by the reaction sequence depicted in Scheme I (**1b** → **5b**). Both procedures start from indoles and allow the synthesis of 2-(alkylthio)tryptophans substituted in the indole nucleus. This is not the case with other approaches reported for 2-(alkylthio)tryptophans, since they are based on derivatization of tryptophan derivatives.[20]

In the approach reported here the 3-acetoxy groups of the indole **10** or **11** serves as an auxillary group, allowing the introduction of a nucleophile at the C(2)-position of the indole nucleus. The migratory aptitude of this acetoxy group in compound **6** (R^2 = OAc) is apparently sufficiently low to prevent C(3) → C(2) migration as observed for alkylthio substituents (cf. **6** → **7**). Our results suggest that the reaction sequence **3** → **8** → **9** is limited to the introduction of soft nucleophiles.

In summary the adduct **3** opens a new approach to indole alkaloids, both in terms of strategy and methodology. Presently, its use as intermediate in the synthesis of the sporidesmins,[21] roquefortines,[22] and tryptoquivalines[22] is being studied.

Experimental Section

Melting points were taken on a Koefler hot stage (Leitz-Wetzlar) and are uncorrected. Ultraviolet spectra were measured with a Perkin-Elmer Model 555 spectrometer.

Proton magnetic resonance spectra were measured on a Varian Associates Model T-60 or a Bruker WH-90 spectrometer. Chemical shifts are reported as δ-values (parts per million) relative to tetramethylsilane as an internal standard. Mass spectra were obtained with a double-focusing VG 7070E spectrometer. Thin-layer chromatography (TLC) was carried out by using Merck precoated silica gel F-254 plates (thickness 0.25 mm). Spots were visualized with a UV hand lamp, iodine vapor, Cl_2–TDM,[23] cinnamaldehyde/HCl for indole detection,[24] $AgNO_3/Na_2CrO_7$ for the detection of sulfides,[25] or ninhydrin. A miniprep LC (Jobin Yvon) was used for preparative HPLC; Merck silica gel H (type 60) was used as the stationary phase. Merck silica gel (type 60) was used for flash chromatography.

3-(Ethoxycarbonyl)-4a-acetoxy-4,4a,9,9a-tetrahydro-1,2-oxazino[5,6-*b*]indole (13) and Ethyl α-(Hydroxyimino)-β-(3-acetoxyindolen-3-yl)propanoate (15). To a stirred solution of 3-acetoxyindole (**10**) (Aldrich Chemical Co.; 1 mmol, 0.18 g) and a suspension of dry Na_2CO_3 (2 mmol, 0.22 g) in dry CH_2Cl_2 (10 mL) was added dropwise a solution of ethyl α-(hydroxyimino)-β-bromopropanoate (1.5 mmol, 0.32 g) in dry CH_2Cl_2 (15 mL) at room temperature and in an argon atmosphere. The reaction was monitored by TLC ($MeOH/CH_2Cl_2$, 4/96, v/v) until completion. After 18 h, the reaction mixture was filtered through a thin layer of silica gel and then evaporated to yield the oily products **13** (85%) and **15** (15%). These could be separated by flash column chromatography to give pure products. The compounds appeared to be unstable when stored in solution (CH_2Cl_2).

Compound 13: R_f 0.5 ($MeOH/CH_2Cl_2$, 4/96, v/v); EIMS (70 eV), *m/e* (relative intensity) 304 ($[M]^+$, 5), 262 (11), 245 ($[M - C_2H_3O_2]^+$, 10), 231 ($[M - C_3H_5O_2]^+$, 5), 145 (100); exact mass calcd for $C_{15}H_{16}N_2O_5$ 304.1059, found 304.1065; ^1H NMR (60 MHz, $CDCl_3$) δ 7.6–6.6 (m, 4 H, indoline C(4)–C(7) *H*), 5.9 (br s), 1 H, indoline N*H*), 5.7 (d, ^3J = 1 Hz, 1 H, indoline C(2) *H*), 4.3 (q, 2 H, CCH_2CH_3), 3.6 and 3.2 (AB spectrum, $^2J_{AB}$ = 16 Hz, 2 H, indoline (C(3)CH_2), 2.0 (s, 3 H, $COCH_3$), 1.3 (t, 3 H, OCH_2CH_3).

Compound 15: R_f 0.2 ($MeOH/CH_2Cl_2$, 4/96, v/v); EIMS (70 eV), *m/e* (relative intensity) 304 ($[M]^+$, 3%), 274 (6%), 145 (44%), 54 (100%); exact mass calcd for $C_{15}H_{16}N_2O_5$ 304.1059, found 304.1058; ^1H NMR (60 MHz, $CDCl_3$) δ 7.5–6.5 (m, 4 H, indolenine C(4)–C(7)*H*), 5.8 (s, 1 H, indolenine C(2)*H*), 4.5 (br s), 1 H, NOH), 4.25 (dq, 2 H, OCH_2CH_3), 3.6 and 3.0 (AB spectrum, $^2J_{AB}$ 15 Hz, 2 H, indolenine C(3)CH_2), 2.0 (s, 3 H, $COCH_3$), 1.3 (t, 3 H, OCH_2CH_3).

3-(Ethoxycarbonyl)-4a-acetoxy-4,4a,9,9a-tetrahydro-9-methyl-1,2-oxazino[5,6-*b*]indole (14). To a stirred solution of 3-acetoxy-*N*-methylindole[7] (**11**) (2 mmol, 0.38 g) and a suspension of dry Na_2CO_3 (4 mmol, 0.44 g) in dry CH_2Cl_2 (20 mL) was added dropwise a solution of ethyl α-(hydroxyimino)-β-bromopropanoate (2.2 mmol, 0.46 g) in dry CH_2Cl_2 (20 mL). After stirring for 6 h at room temperature and in an argon atmosphere the solids were filtered off through a thin layer of silica gel, after which the solvent was evaporated. The residue was subjected to flash column chromatography (silica gel 60; $MeOH/CH_2Cl_2$, 2/98, v/v) to give **14** in 90% yield (0.57 g) as an oil which was homogeneous on TLC: R_f 0.35 (CH_2Cl_2); EIMS (70 eV), *m/e* (relative intensity) 318 ($[M]^+$, 2%), 276 (6), 185 (15), 159 ($[C_{10}H_9NO]^+$, 100); exact mass calcd for $C_{16}H_{18}N_2O_5$ 318.1216, found 318.1214; ^1H NMR (60 MHz, $CDCl_3$) δ 7.4–6.2 (m, 4 H, indoline C(4)–C(7)H), 5.5 (s, 1 H, indoline C(2)H), 4.15 (q, 2 H, OCH_2Cl_3), 3.6 and 3.0 (AB spectrum, $^2J_{AB}$ = 15 Hz, 2 H, indoline C(3)-CH_2), 2.95 (s, 3 H, indoline NCH_3), 2.0 (s, 3 H, $COCH_3$), 1.2 (t, 3H, OCH_2CH_3).

Ethyl α-(Hydroxyimino)-β-[2-(methylthio)indol-3-yl]-propanoate (9a). $NaSCH_3$ (6 mmol, 0.42 g) was added to a solution of the adduct **13**—freshly prepared from 5 mmol (0.88 g) of 3-acetoxyindole (**10**)—in dry CH_2Cl_2 (50 mL) at 0 °C and in an argon atmosphere. Subsequently, CF_3COOH (12 mmol, 1.25 g) in dry CH_2Cl_2 (50 mL) was added dropwise. After 3 h the reaction mixture was neutralized with $NaHCO_3$. The suspension was filtered; the filtrate was washed with brine and dried with Na_2SO_4. Evaporation of the solvent gave a residue which was chromatographed (silica gel 60H; $MeOH/CH_2Cl_2$, 2/98, v/v) to give **9a** in 68% (0.98 g) yield (calculated on **10**). The compound was homogeneous on TLC (R_f 0.6; $MeOH/CH_2Cl_2$, 6/94, v/v). Spectroscopical data were identical with those reported previously.[6]

Ethyl α-(Hydroxyimino)-β-[2-(ethylthio)indol-3-yl]-propanoate (9b). Ethanethiol (6 mmol, 0.37 g) was added to a solution of the adduct **13**—freshly prepared from 5 mmol (0.88 g) of 3-acetoxyindole (**10**)—in dry CH_2Cl_2 (50 mL) at 0 °C in an argon atmosphere. Subsequently, CF_3COOH (6 mmol, 0.68 g) in dry CH_2Cl_2 (10 mL) was added dropwise. After 3 h the reaction mixture was neutralized with $NaHCO_3$. The suspension was filtered; the filtrate was washed with brine and dried with Na_2SO_4. Evaporation of the solvent gave a residue which was chromatographed (silica gel 60H; $MeOH/CH_2Cl_2$, 2/98, v/v) to give **9b** in 70% (0.43 g) yield (calculated on **10**). Spectroscopical data were

(19) α-Oximino carboxylic acid derivatives can be reduced selectively to the corresponding *N*-hydroxyamino acids with $Me_3N{\cdot}BH_3$; see ref 6.

(20) (a) Savige, W. E.; Fontana, A. *Int. J. Peptide Protein Res.* **1980**, *15*, 102; *Chem. Commun.* **1976**, 600. (b) Faulstich, H.; Wieland, Th.; Jochum, C. *Liebigs Ann. Chem.* **1968**, *713*, 186. (c) Fontana, A.; Scoffone, E. *Methods Enzymol.* **1972**, *25*, 482. (d) Ohno, M.; Tanaka, S.; Shieh, T.; Spande T. F. *J. Org. Chem.* **1984**, *49*, 5069.

(21) For recent reviews see: Mortimer, P. A.; Ronaldson, J. W. In *Plant and Fungal Toxins*; *Handbook of Natural Toxins 1*, Keeler, R. F., Tu, A. T., Eds.; M. Dekker: New York, 1983; p 361. Nagarajan, R. In *Mycotoxins - Production, isolation, separation and purification*, Betina, V., Ed.; Elsevier Science: Amsterdam, 1984; p 351.

(22) For a recent review, see: *Fungal Metabolites II*; Turner, W. B., Aldridge, D. L., Eds.; Academic: New York, 1983; p 405.

(23) von Arx, E.; Faupel, M.; Bruggen, M. *J. Chromatogr.* **1976**, *120*, 224.

(24) *Anfaerbereagentien fuer Duennschicht- und Papierchromatographie*; Fa Merck: Darmstadt, FRG, 1970; p 108.

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identical with those reported previously.[6]

Ethyl α-(Hydroxyimino)-β-[2-((3-methyl-2-butenyl)thio)indol-3-yl]propanoate (9c). Compound **9c** was obtained from 3-methyl-2-butenethiol[26] (10 mmol, 1.02 g) and the adduct **13**—freshly prepared from 5 mmol (0.88 g) of 3-acetoxyindole (**10**) as described for the preparation of **9b**. Preparative HPLC (silica gel 60H; MeOH/CH_2Cl_2, 0.5/99.5, v/v) gave **9c** in 64% (1.11 g) yield after recrystallization from CH_2Cl_2/*n*-hexane: R_f 0.33 (MeOH/CH_2Cl_2, 3/97, v/v); mp 112.5–113.5 °C; UV (MeOH) λ_{max} 298 (sh), 290, 283 (sh), 221 nm; λ_{min} 255 nm; EIMS (70 eV), *m/e* (relative intensity) 346 ($[M]^+$, 38), 261 ($[C_{13}H_{13}N_2O_2S]^+$, 100), 188 ($[C_{10}H_8N_2S]^+$, 23), 162 ($[C_9H_8NS]^+$, 26), 161 (30%), exact mass calcd for $C_{18}H_{22}N_2O_3S$ 346.1351, found 346.1354; ^1H NMR (90 MHz, $CDCl_3$) δ 9.64 (br s, 1 H, NOH), 8.09 (br s), 1 H, indole NH), 7.73–6.92 (m, 4 H, indole C(4)–C(7)*H*), 5.33 (m, ^3J = 8 Hz, ^4J = 1 Hz, 1 H, SCH_2CH=), 4.24 (s, 2 H, indole C(3)CH_2), 4.23 (q, 2 H, OCH_2CH_3), 3.41 (d, ^3J = 8 Hz, 2 H, SCH_2CH=), 1.70 and 1.37 (2 × s, 6 H, C=$(CH_3)_2$), 1.26 (t, 3 H, OCH_2CH_3).

Ethyl α-(Hydroxyimino)-β-{[2-*S*-(*N*-acetyl-L-cysteinyl methyl ester)]indol-3-yl}propanoate (9d) and Ethyl α-(Benzyloximino)-β-(oxindol-3-yl)propanoate (18). Compound **9d** was prepared from *N*-acetyl-L-cysteine methyl ester (8 mmol, 1.42 g) and the adduct **13**—freshly prepared from 7 mmol (1.23 g) of 3-acetoxyindole (**10**)—as described for the preparation of **9b**. The reaction mixture was neutralized after 20 h. HPL chromatography (silica gel 60H, MeOH/CH_2Cl_2, 2/98, v/v) and subsequent recrystallization (ethyl acetate/*n*-hexane) gave **9d** (1.79 g) in 61% yield: mp 135–136 C (CH_2Cl_2/*n*-hexane); R_f 0.3 (MeOH/CH_2Cl_2, 4/96, v/v). Spectroscopical data were identical with those reported previously.[6] As byproduct we isolated **18** in 5% (90 mg) yield: mp 186–188 °C (CH_2Cl_2/*n*-hexane); R_f 0.25 (MeOH/CH_2Cl_2, 4/96, v/v); CIMS (70 eV), *m/e* (relative intensity) 263 ($[MH]^+$, 28), 146 ($[C_9H_8NO]^+$, 20), exact mass calcd for $C_{13}H_{15}N_2O_4$ 263.1032, found 263.1030; ^1H NMR (90 MHz, $CDCl_3$) δ 9.70 (br s) 1 H, oxindole NH), 8.25 (br s, 1 H, N O*H*), 7.35–6.80 (m, 4 H, oxindole C(4)–C(7)*H*), 4.32 (q, 2 H, OCH_2CH_3), 3.97 (t, ^3J = 8.5 Hz, 1 H, oxindole C(3)*H*), 3.65 (d, ^3J = 8.5 Hz, 2 H, oxindole C(3)CH_2) 1.33 (t, 3H, OCH_2CH_3).

Ethyl α-(Hydroxyimino)-β-{[2-(*N*-acetyl-L-cysteinyl methyl ester)]-*N*-methylindol-3-yl}propanoate (9e). Compound **9e** was prepared from *N*-acetyl-L-cysteine methyl ester (1.2 mmol, 0.21 g) and the adduct **14**—freshly prepared from 1 mmol (0.32 g) of 3-acetoxy-*N*-methylindole **11**—in dioxane–hydrogen chloride solution (dioxane/dioxane–HCl saturated, 10/2, v/v) at 0 °C and in an argon atmosphere. After 1 h the reaction mixture was neutralized with $NaHCO_3$, filtered, and evaporated. The residue was dissolved in CH_2Cl_2, washed with brine, dried (Na_2SO_4), and filtered and the solvent evaporated. Flash column chromatography (silica gel 60; MeOH/CH_2Cl_2, 2/98, v/v) gave **9e** in 74% yield (0.32 g) as a foam which was homogeneous on TLC: R_f 0.5 (MeOH/CH_2Cl_2, 6/94, v/v); UV (MeOH) λ_{max} 298 (sh), 290, 283 (sh), 221 nm; λ_{min} 255 nm; EIMS (70 eV), *m/e* (relative intensity) 435 ($[M]^+$, 13), 275 (17), 144 ($[C_{16}H_{10}NO_3]^+$, 100); exact mass calcd for $C_{20}H_{25}N_3O_6S$ 435.1464; found 435.1469; ^1H NMR (90 MHz, $CDCl_3$) δ 7.65–6.90 (m, 4 H, indole C(4)–C(7)*H*), 6.80 (br d, ^3J = 7.5 Hz, 1 H, CON*H*), 4.81 (X part of ABX spectrum, $^3J_{AX}$ = 4.8 Hz, $^3J_{BX}$ = 4.8 Hz, $^3J_{XNH}$ = 7.5 Hz, 1 H, SCH_2CH), 4.24 (q, 2 H, OCH_2CH_3), 4.20 (s, 2 H, indole C(3)CH_2), 3.81 (s, 3 H, $COCH_3$), 3.43 (s, 3 H, NCH_3), 3.26 and 3.21 (AB part of ABX spectrum, $^3J_{AX}$ = $^3J_{BX}$ = 4.8 Hz, 2 H, SCH_2CH_3), 1.84 (s, 3 H, $COCH_3$), 1.25 (t, 3 H, OCH_2CH_3).

Ethyl α-(Hydroxyimino)-β-(*N*-methylindol-3-yl)-propanoate (9f). A solution of HCl in dioxane (10 mL of a 7 N solution) was added to a stirred solution of the adduct **14**—freshly prepared from 5 mmol (1.59 g) of 3-acetoxy-*N*-methylindole 11–and trimethylamine borohydride (Aldrich Chemical Co., 5.5 mmol, 0.40 g) in dioxane (25 mL) at 0 °C and in an argon atmosphere. After being stirred for 1 h at room temperature, the reaction mixture was neutralized with $NaHCO_3$ and filtered and the solvent evaporated. The residue was subjected to flash column chromatography (Merck silica gel 60; MeOH/CH_2Cl_2, 1/99, v/v) to give 1.20 g (91%) of crystalline **9f**, which was recrystallized from CH_2Cl_2/n-hexane; mp 119–120 °C; spectroscopic data are identical with those reported previously.[1]

Ethyl α-(Hydroxyimino)-β-(3-(ethoxycarbonyl)-4,4a-dihydro-1,2-oxazino[5,6-*b*]indol-3-yl)propanoate (17). A solution of **13** (0.5 mmol, 0.15 g) in CH_2Cl_2 (10 mL) was treated with CF_3COOH (0.1 mmol, 100 mg) in CH_2Cl_2 (10 mL). After 2 days the reaction was neutralized with $NaHCO_3$, filtered, washed with brine, dried (Na_2SO_4), and filtered and the solvent evaporated. Flash column chromatography (CH_2Cl_2) gave **17** as the major product (ca 50%) as an oil which was homogeneous on TLC: R_f 0.6 (MeOH/CH_2Cl_2, 3/97, v/v); EIMS (70 eV), *m/e* (relative intensity) 373 ($[M]^+$, 8), 258 (32), 173 (51), 143 (100); exact mass calcd for $C_{18}H_{19}N_3O_6$ 373.1274, found 373.1271; UV (MeOH) λ_{max} 298, 239, 204 nm; λ_{min} 271, 223 nm; ^1H NMR (90 MHz, $CDCl_3$) δ 7.48–6.51 (m, 4 H, indolenine C(4)–C(7)*H*), 4.95 (s, 1 H, NO*H*), 4.38 and 4.31 (2 × q, 4 H, 2 × OCH_2CH_3), 4.29 (s, 2 H, indolenine C(3)H_2), 4.12 and 3.54 (AB spectrum, $^2J_{AB}$ = 18.7 Hz, 2 H, indolenine C(3)CH_2), 1.40 and 1.36 (2 × t, 6 H, 2 × OCH_2CH_3),

Ethyl α-(Benzyloximino)-β-[2-(methylthio)-3-(3-methyl-2-butenyl)indolen-3-yl]propanoate (23a) and Ethyl α-(Benzyloximino)-β-[2-((3-methyl-2-butenyl)thio)-3-(3-methyl-2-butenyl)indolen-3-yl]propanoate (24). Ethyl α-(Benzyloximino)-β-[2-((3-methyl-2-butenyl)thio)indol-3-yl]-propanoate. Benzyl bromide (1.1 mmol, 0.19 g) was added dropwise to a stirred solution of **9c** (1.0 mmol, 0.35 g) and potassium *tert*-butoxide (1.0 mmol, 0.115 g) in dimethoxyethane (10 mL) in an argon atmosphere. After 3 h the reaction mixture was filtered and evaporated. Subsequent HPL chromatography (MeOH/CH_2Cl_2, 0.25/99.75, v/v) gave in 76% yield (0.33 g) the *O*-benzyl derivative of **9c** which was homogeneous on TLC: R_f 0.65 (MeOH/CH_2Cl_2, 1/99, v/v); EIMS (70 eV), *m/e* (relative intensity) 436 ($[M]^+$, 28), 261 ($[C_{13}H_{13}N_2O_2S]^+$, 69), 162 ($[C_9H_8NS]^+$, 28), 149 (31), 91 ($[C_7H_7]^+$, 100%); exact mass calcd for $C_{25}H_{28}N_2O_3S$ 436.1821, found 436.1821; ^1H NMR (90 MHz, $CDCl_3$) δ 8.04 (br s, 1 H, indole N*H*), 7.49–6.79 (m, 4 H, indole C(4)–C(7)*H*), 7.27 (s, 5 H, C_6H_5), 5.29 (s, 2 H, O-$CH_2C_6H_5$), 5.24 (m, 1 H, ^3J = 8.1 Hz, ^4J = 0.9 Hz, CH_2-C*H*=C), 4.18 (q, 2 H, ^3J = 7.0 Hz, -OCH_2CH_3), 4.18 (s, 2 H, indole C(3)CH_2), 3.29 (d, 2 H, ^3J = 8.1 Hz, S-CH_2), 1.64 (s, 3 H, CH=$(CH_3)CH_3$), 1.31 (d, 3 H, ^4J = 0.9 Hz, CH=C$(CH_3)CH_3$), 1.18 (t, 3 H, ^3J = 7.1 Hz, OCH_2CH_3).

To a stirred solution of the *O*-benzyl derivative of **9c** (0.44 mol, 0.19 g) in methyl iodide (5 mL) was added HgI_2[17] (0.44 mmol, 0.20 g) at 0 °C and in an argon atmosphere. The mixture was stirred for 2 days at room temperature. Evaporation of the solvent and careful HPL chromatography (silica gel 60H; MeOH/CH_2Cl_2, 0.5/99.5, v/v) gave the oily compounds **23a** (25%, 49 mg) and **24** (13%, 29 mg), which were homogeneous on TLC.

Compound 23a: R_f 0.06 (MeOH/CH_2Cl_2, 0.5/99.5, v/v); UV (MeOH) λ_{max} 300 (sh), 290 (sh), 280, 216 (sh), 203 nm, λ_{min}=259 nm; EIMS (70 eV), *m/e* (relative intensity) 450 ($[M]^+$, 55), 382 ($[C_{21}H_{22}N_2O_3S]^+$, 23), 275 ($[C_{14}H_{15}N_2O_2S]^+$, 17), 176 ($[C_{10}H_{10}NS]^+$, 30), 91 ($[C_7H_7]^+$, 100%; exact mass calcd for $C_{26}H_{30}N_2O_3S$ 450.1977, found 450.1982, ^1H NMR (90 MHz, $CDCl_3$) δ 7.47–6.87 (m, 4 H, indolenine C(4)–C(7)*H*), 7.28 (s, 5 H, C_6H_5), 5.14 (s, 2 H, $OCH_2C_6H_5$), 4.42 (m, 1 H, ^3J = 7.0 Hz, ^4J = 1.4 Hz, CH_2CH=), 4.09 (q, 2 H, OCH_2CH_3), 3.29 and 2.97 (AB spectrum, $^2J_{AB}$ = 13.0 Hz, indolenine C(3)CH_2–), 2.53 (s, 3 H, SCH_3), 2.49 (d, 2 H, ^3J = 7.0 Hz, CH_2-CH=), 1.42 (s, 6 H, =C$(CH_3)_2$, 1.18 (t, 3 H, OCH_2CH_3).

Compound 24: R_f 0.13 (MeOH/CH_2Cl_2, 0.5/99.5, v/v); UV (MeOH) λ_{max} 300 (sh), 291 (sh), 282, 220 (sh), 204 nm, λ_{min} 259 nm; EIMS (70 eV), *m/e* (relative intensity) 504 ($[M]^+$, 23), 435 ($[C_{25}H_{27}N_2O_3S]^+$, 28), 329 ($[C_{18}H_{21}N_2O_2S]^+$, 15), 261 ($[C_{13}H_{13}N_2O_2S]^+$, 28), 91 ($[C_7H_7]^+$, 100); ^1H-NMR (90 MHz, $CDCl_3$) δ 7.36–6.82 (m, 4 H, indolenine C(4)–C(7)*H*), 7.16 (s, 5 H, C_6H_5), 5.29 (m, 1 H, ^3J = 8 Hz, ^4J = 2 Hz, SCH_2CH=), 5.11 (s, 2 H, $OCH_2C_6H_5$), 4.40 (m, 1 H, ^3J = 6 Hz, indolenine (C(3)-CH_2CH=), 4.09 (q, 2 H, OCH_2CH_3), 3.89 and 3.79 (AB spectrum, J_{AB} = 4 Hz, 2 H, SCH_2CH=), 3.26 and 2.94 (AB spectrum, $^2J_{AB}$ = 13 Hz, 2 H, indolenine C(3)-CH_2), 2.51 (t, ^3J = 6 Hz, 2 H, indolenine C(3)CH_2CH=), 1.73 (s, 6 H, SCH_2CH=C$(CH_3)_2$), 1.42 (s, 6 H, indolenine C(3)CH_2CH=C$(CH_3)_2$), 1.17 (t, 3 H, OCH_2CH_3).

Ethyl α-(Benzyloximino)-β-[2-(ethylthio)-3-(3-methyl-2-butenyl)indolen-3-yl]propanoate (23b), Ethyl α-(Benzyloximino)-β-[2-(ethylthio)-*N*-(3-methyl-2-butenyl)indol-3-

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yl]propanoate (25), and Ethyl α-(Benzyloximino)-β-[2-(ethylthio)-3-(1,1-dimethyl-2-propenyl)indolen-3-yl]-propanoate (26). Ethyl α-(Benzyloximino)-β-[2-(ethylthio)indol-3-yl]propanoate. A solution of benzyl bromide in dimethoxyethane (1 mL) was added dropwise to a stirred solution of **9b** (1.5 mmol, 0.46 g) in dimethoxyethane (10 mL) at room temperature. Stirring in an argon atmosphere was continued for 4 h at room temperature. Then the solvent was removed in vacuo. A solution of the residue in CH_2Cl_2 was washed with 1 N HCl and with brine and subsequently dried over Na_2SO_4. The residue obtained by evaporation of the solvent was subjected to flash column chromatography (CH_2Cl_2) to give the *O*-benzyl derivative of **9b** in 74% (0.44 g) yield. Spectroscopical data are identical with those reported previously.[6]

Dimethylallyl bromide (2.5 mmol, 0.350 g) was added portionwise to a solution of the *O*-benzyl derivative of **9b** (0.25 mmol, 0.099 g) and suspension of K_2CO_3 (0.25 mmol, 0.035 g) in dry acetone (10 mL). After 2 weeks the reaction mixture was filtered and the solvent evaporated. Flash column chromatography gave **25** (48%, 0.056 g) and a mixture of **23b** and **26** in a ratio of 3:2 (41%, 0.047 g). HPL-chromatography of the latter fraction gave **26** slightly contaminated with **23b** and pure **23b**.

Compound 23b: oil, homogeneous on TLC, R_f 0.53 ($MeOH/CH_2Cl_2$, 1/99, v/v); UV (MeOH) λ_{max} 304 (sh), 291 (sh), 282, 218 (sh), 202 nm, λ_{min} 258 nm; EIMS (70 eV), *m/e* (relative intensity) 464 ($[M]^+$, 61), 396 ($[C_{22}H_{24}N_2O_3S]^+$, 36), 357 ($[C_{20}H_{25}N_2O_2S]^+$, 10), 289 ($[C_{15}H_{17}N_2O_2S]^+$, 29), 190 ($[C_{11}H_{12}NS]^+$, 28), 215 (26), 91 ($[C_7H_7]^+$, 100); exact mass calcd for $C_{27}H_{32}N_2O_3S$ 464.2134, found 464.2128; ^1H NMR (90 MHz, $CDCl_3$) δ 7.49–6.91 (m, 4 H, indolenine C(4)–C(7)*H*), 7.33 (s, 5 H, C_6H_5), 5.18 (s, 2 H $OCH_2C_6H_5$), 4.40 (m, 1 H, ^3J = 6 Hz, indolenine C(3)CH_2CH=), 4.11 (q, 2 H, OCH_2CH_3), 3.23 (q, 2 H, S-CH_2CH_3), 3.26 and 2.94 (AB spectrum, $^2J_{AB}$ = 12.6 Hz, 2 H, indolenine C(3)CH_2), 2.53 (m, 2 H, indolenine C(3)CH_2CH=), 1.43 (s, 6 H, CH=C(CH_3)$_2$), 1.37 (t, 3 H, SCH_2CH_3), 1.18 (t, 3 H, OCH_2CH_3).

Compound 25: oil, homogeneous on TLC, R_f 0.75 ($MeOH/CH_2Cl_2$, 1/99, v/v); UV (MeOH) λ_{max} 293 (sh), 285, 224, 202 nm, λ_{min} 259, 213 nm; EIMS (70 eV), *m/e* (relative intensity) 464 ($[C_{27}H_{32}N_2O_3S]^+$, 56), 357 ($[C_{20}H_{25}N_2O_2S]^+$, 8), 258 ($[C_{16}H_{20}NS]^+$, 6), 190 ($[C_{11}H_{12}NS]^+$, 26), 149 (36), exact mass calcd for $C_{27}H_{32}N_2O_3S$ 464.2134, found 464.2129; ^1H NMR (90 MHz, $CDCl_3$) δ 7.49–6.84 (m, 4 H, indole C(4)–C(7)*H*), 7.22 (s, 5 H, C_6H_5), 5.24 (s, 2 H $OCH_2C_6H_5$), 5.09 (m, ^3J = 6 Hz, ^4J = 1 Hz, NCH_2CH=C), 4.89 (d, 2 H, ^3J = 6 Hz, NCH_2CH=), 4.20 (s, 2 H, indole C(3)CH_2), 4.12 (q, 2 H, OCH_2iCH_3), 2.62 (q, 2 H, SCH_2CH_3), 1.84 (d, ^4J = 1 Hz, 3 H, -CH=C(CH_3)CH_3), 1.66 (d, ^4J = 1 Hz, 3 H, -CH=C(CH_3)CH_3), 1.17 (t, 3 H, SCH_2CH_3), 1.11 (t, 3 H, OCH_2CH_3).

Compound 26: ^1H NMR (90 MHz, $CDCl_3$) δ 7.42–6.79 (m, 4 H, indolenine C(4)–C(7)*H*), 7.30 (s, 5 H, C_6H_5), 6.11 (X part of ABX spectrum, $^3J_{trans}$ = 16 Hz, $^3J_{cis}$ v 11 Hz, 1 H, $C(CH_3)_2CH_x$ = CH_AH_B), 5.09 (s, 2 H, $CH_2C_6H_5$), 5.09 and 5.01 (AB part of ABX spectrum, $^3J_{trans}$ = 16 Hz, $^3J_{cis}$ = 11 Hz, $C(CH_3)_2CH_x$=CH_{AHB}), 4.02 (q, 2 H, OCH_2CH_3), 3.76 and 3.52 (AB spectrum, $^2J_{AB}$ = 9 Hz, 2 H, indolenine C(3)CH_2), 3.20 (q, 2 H, SCH_2iCH_3), 1.32 (t, 3 H, SCH_2CH_3), 1.08 (t, 3 H, OCH_2CH_3), 1.04 and 0.99 (s, 6 H, indolenine C(3)C(CH_3)$_2$).

O-Acylation of α-Diazo Ketones. A Novel Route to Alkenediazonium and 1,3-Dioxolium Salts

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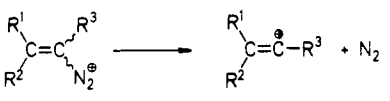
O-Acylation of α-diazo ketones with benzoyl triflate or diphenylacetyl triflate generates the corresponding β-(acyloxy)alkenediazonium salts **5** and **15**. These thermolabile compounds can be trapped with isopropylamine at low temperature to give triazoles **21**. Dediazoniation of **5** and **15** leads to 1,3-dioxolium salts **7** and **16** as well as small amounts of vinyl triflates **8** and **17** via intermediary vinyl cations. O-Benzoylation with benzoyl triflate has also been realized for the quinoid α-diazo ketone **9**; the resulting diazonium salt **10** gives triazole **13** on treatment with isopropylamine.

Introduction

Alkenediazonium salts **1** have been generated, either as reactive intermediates or as isolable compounds, by a



1 **2**

number of synthetic routes.[1] Starting from alkyl diazoacetates or α-diazoacetamides, stable ethenediazonium salts were obtained by O-alkylation with Meerwein salts.[1] α-Diazo ketones seem not to have been subjected to such a procedure, but the reaction product from ω-diazoacetophenone and $PCl_4^+SbCl_6^-$ clearly results from O-alkylation of the diazo ketone by an intermediarily generated alkyl cation.[2] We have recently found that triflic anhydride reacts with azibenzils to give vinylene bis(trifluoromethanesulfonates) via initial electrophilic attack of a CF_3SO_2 group on the carbonyl oxygen of the ambident α-diazo ketone; ethenediazonium salts are merely intermediates in the reaction sequence.[3] Successful O-alkylations and O-sulfonylations of α-diazo ketones suggest that acylation reactions will also be feasible, provided the acylating reagent has a sufficiently high electrophilicity. For our study, we chose acyl triflates which have already been introduced as superior electrophilic acyl transfer reagents.[4] They supersede by far the conventional acylating reagents such as acyl halides and carboxylic anhydrides in terms of efficiency and mildness of the reaction conditions. Their high acylation potential has been testified by Friedel–Crafts acylation of the aromatic nucleus in the absence of a Lewis acid catalyst,[4,5] by electrophilic

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