Approaches to Analogs of Anhydrogliotoxin

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Abstract: The addition of α-halo-α-aminoacyl chlorides to ethyl indolenine-2-carboxylates followed by reaction with sulfur nucleophiles and a final ring closure provides a convenient and new synthetic scheme to analogs of gliotoxin, the simplest of the natural products containing the epidithiodiketopiperazine system. Illustrative of this approach, adducts of ethyl 3,3-dimethylindolenine-2-carboxylate (17) with acid chlorides, α-halo acid chlorides, and N-trifluorooacetyl-α,α-dichlorosarcosyl chloride (44) have been studied. The last adduct when treated with a sulfide-polythiodiketopiperazine nuear gave a monothiodiketopiperazine 49 (30% yield) but no disulfide 50. Reduction of 49 with NaCNBH₃ proceeded stereoselectively to afford mainly the secogliotoxin analog 51 in addition to the diastereoisomer 52. Cyclization of this mixture presumably led to the strained epimonothiodiketopiperazine 41, which easily opened to the isomeric lactam 55 in addition to lactam 56 formed by epimerization.

The number of natural products containing the epidithiodiketopiperazine ring 1 continues to grow with the recent reports on the two fungal metabolites chaetocin (2) and verticillin A (3). Both are highly active against gram-positive bacteria. Chaetocin is cytotoxic but lacks antiviral activity, while verticillin A is cytotoxic and active against mycobacteria. Other members of this group of fungal metabolites are the sporidesmins A through G (4-6) several of which possess potential antibacterial activity, the aranotins (7-9) and apoaranotins (10-11) which have no antibacterial but do have potent antiviral activity, gliotoxin (12), an antibiotic, antifungal and antiviral agent, and dehydrogliotoxin (12b) with antibacterial activity.

Two other fungal metabolites, chetomin (C₆H₃N₃O₄S₂) and oryzachlorin (C₆H₃N₃O₄S₂Cl), of un-known structure, probably contain the epidithiodike-topiperazine ring. The former is active against gram-positive bacteria and viruses while the latter has only antifungal and antiviral activity.

The mechanism of antiviral action of gliotoxin and orranotin depends upon the specific inhibition of RNA-dependent DNA polymerases from tumor-producing viruses or blocking of the synthesis of viral RNA in the case of chetomin.

Several syntheses of simple epidithiodiketopiperazines have been reported, which feature the addition of sulfur substituents to a preformed diketo-piperazine. Surprisingly, the simple model 1a is highly active in inhibiting viral RNA synthesis, in support of the view that the activity of the more complex natural products resides in the epidithiodiketo-piperazine ring.

Another approach to this ring system started with 2-benzamido-2-mercaptopropanoic acid (13) as a possible precursor.

The drastic reaction conditions of all of these methods preclude their successful extension to the polycyclic epidithiodiketopiperazines. A synthetic approach of general applicability, we felt, would feature the initial construction of the disulfide bridge and then ring closure to a bridged diketopiperazine.

The addition of acyl chlorides to indolenines (Chart I), a reaction first reported by Leuchs, who studied compounds 14-16, served as our first step.

The 2-chloro substitutent in Leuchs' adducts 18-20 is known to undergo easy nucleophilic displacement, and

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(15) J. W. Moncrief, ibid., 90, 6517 (1968).
The reaction of sulfur nucleophiles (e.g., \( \text{SCOCH}_3^-, \text{SCN}^-, \text{S}_2\text{O}_3^{2-} \), etc) on the adduct 21 derived from 17 was first investigated as a route to 1-acylindoline-2-carboxylic acid derivatives having a thio function in the 2 position. The indolenine ester 17 was prepared as outlined in Chart II.

Chart II

The azo ester 23, when prepared from ethyl \( \alpha \)-isopropylacetooacetate and benzenediazonium chloride under mildly alkaline conditions, was stable enough to permit isolation. Careful treatment with ethanolic solutions of sodium hydroxide or preferably ammonium hydroxide gave the hydrazone ester 24, which was converted into 17 by refluxing in HCl-saturated ethanol. The yields are much higher than reported in the published procedure\(^1\) where the coupling and hydrazone formation were carried out in a single step.

formation steps are carried out under such strongly alkaline conditions that only the hydrazone 25 can be isolated. This, on Fischer cyclization, gives a mixture of 17 and 26 accompanied by 2,3-dimethylindole, the product of decarboxylation and rearrangement of 26. The indolenine 17 can also be prepared by refluxing 23 in absolute alcoholic hydrogen chloride. This indicates that the transformation (23 -> 24) in the Japp-Klingemann reaction can also be acid catalyzed.

We first examined the reaction of 17 with simple acid chlorides, such as acetyl chloride and chloroacetyl chloride, and found that when freshly purified reagents were employed, the Leuchs addition proceeded in high yield at room temperature. Interestingly, this is the first instance of addition of acyl chlorides to an indolene-2-carboxylic acid derivative, the previous examples being limited to indolene with 2-hydrogen, 2-methyl, or 2-phenyl substituents. The indolenine 17 is less reactive than unconjugated ones, since benzoyl chloride could not be added. Reaction of 17 with ethoxycarbonyl chloride or benzoxycarbonyl chloride was very slow, and trifluoroacetyl chloride did not react at all.

Two isomeric thioacetates, 28 and 29, were isolated when potassium thioacetate was allowed to react with the product from acetyl chloride and 17 which had been allowed to warm to 40°, presumably as the result of a Plancher rearrangement (21 -> 27, Chart III). With potassium thiocyanate on 21, the 2-isothiocyanato compound 30 (Chart IV) was isolated instead of the expected 2-thiocyanato compound.33

When 21 was dissolved in ethanol, it was rapidly converted to the ethyl ether 31, a reaction analogous to the action of methanol on the reaction product from acetyl chloride and benzylidenemethylamine.34

When 32, the product from chloroacetyl chloride and 17, was allowed to react with thiourea, both chlorine atoms were displaced and a bisisothiouronium salt 33 resulted (Chart V). Ordinarily, chloroacetyl groups are removed by thiourea in refluxing aqueous ethanol at pH 5 with the formation of pseudothiodyantoin.36,37 Therefore, we expected the 2-isothioureido derivative 34, but, under these conditions, isolated starting material 17.

The pKₐ of 33 was measured and found to be 7.7. When the solvolysis of 33 was attempted at pH 9.5 in the hope that 34 might be more stable as a neutral species, still only 17 was isolated. This suggests that unacetylated indolene-2-thiols are inherently unstable. Likewise, 2-indolinols are known only as N-acyl or N-alkyl derivatives.32 At least these reactions prove that no Plancher rearrangement occurs at room temperature during acyl chloride additions or subsequent displacement reactions.

When 32 reacted with inorganic sulfides, such as ammonium sulfide, sodium mono-, di-, or tetrasulfide, or thiocarbonate, two products resulted: a mono- (37)
and a disulfide (38) in yields varying with the reactant
(Chart VI). Sodium sulfide and sodium thiocarbonato
gave mainly the monosulfide 37 (ca. 40% yield), whereas
ammonium sulfide and sodium di- and tetrasulfide,
which all exist as mixtures of mono- and polysulfides,
gave the mono- and disulfide in proportions of 2:1, 1:4,
and 2:7, respectively.

None of the thiol 36 could be detected; this together
with the observation that sodium sulfide gives mainly
(>90%) the monosulfide 37 suggests that 37 as well as
38 arise from an intramolecular displacement of chlo-
rine in the sulphydryl intermediate 35 (n = 1 or 2) and
not via the dithiol 36. A tetrasulfide 39 could not be
detected although such a ring system forms easily in
thio-bridged diketopiperazines.23

Models indicate that a cyclic sulfide is possible only in
structures 37 and 38. For the disulfide, but not the
monosulfide, an alternate structure 40 may be en-
visaged. The disulfide 38, however, could be con-
verted quantitatively into the monosulfide 37 with tri-
phenylphosphine31 as evidence that no rearrangement
occurred in the formation of the disulfide.

The nmr spectra of 37 and 38 show a surprisingly
large difference in the δ value for the aromatic C7 proton
(δ 7.70 and 8.20, respectively), indicative of increased
deshielding by the carbonyl group in 38.

An N-acylated 9-amino analog of 38 on deacylation
might undergo spontaneous ring closure and formation
of the dithio-bridged diketopiperazine 41 (n = 2), an
analogue of dehydrogliotoxin (12b).

Accordingly, N-trifluoroacetyl sarcosine chloride (42)
was prepared from the free acid with thionyl chloride,39
conditions mild enough not to affect the trifluoroacetyl
group.40 When 42 was refluxed in sulfuryl chloride in
an attempt to prepare 43, the α-dichloro acid chloride
44 was isolated. Details on this synthesis as well as
some reactions of this interesting compound have been
reported elsewhere.41

When the addition product from 44 and 17 was allowed
to react with sodium tetrasulfide, a ninhydrin-positive,
crystalline compound was isolated in 30% yield whose
structure agrees with 49 (Chart VII).

Chart VII

As we have proposed elsewhere41 44 may decompose
spontaneously to form 47, which may then react with 17
to give 48 which in turn forms 49 with polysulfide ions
in an intramolecular reaction (pathway A). Alter-
natively, pathway B proceeds via 45, the addition pro-
duct of 44 and 17, which may then react in either or both
of two ways: base-catalyzed hydrolysis of the N-tri-
fluoroacetyl group to yield 49 via 48 (pathway B1) or
removal of the N-trifluoroacetyl group following rea-
tion with polysulfide ions (pathway B2). At the moment,
we lack the definitive evidence necessary for a decision
among these mechanistic possibilities.

We were unable to detect the disulfide 50, possibly be-
cause it is either inherently unstable, or unable to sur-
vive the strongly alkaline conditions of the tetrasulfide
reaction.42

The monosulfide 49 was reduced with sodium cy-
noborohydride44 to the amines 51 and 52 (Chart VIII),
which are secgliotoxin analogs.

The course of the reduction is guided by steric induc-
tion of the carbethoxy group. The nmr spectrum of the
reduction mixture showed two signals for the C8 proton,
at δ 5.65 and 5.29 in the ratio 2:1, respectively, and two
signals at δ 2.54 with a separation of 2 Hz for the N-
methyl group. It is assumed that the C9 proton in the
stereoisomer 52 is more shielded than in 51, so that the
signals at δ 5.65 and 5.29 can be assigned to structures
51 and 52, respectively, of which 51 is the major (66%)
and the diastereomer 52 the minor product (33%). An

(37) This method has been used to convert dehydrogliotoxin (12b)4-8
and sporidesmin (4)6 into monosulfides.
epithiodiketopiperazine can be formed only from 51 in which ester and amine functions are in a cis relationship. A bulkier hydride donor might make the reduction even more stereoselective.

Surprisingly the conversion of 49 into 51 and 52 led to no change in the ir spectrum of the amide carbonyl absorption (1705 cm⁻¹). This suggests that conjugation in O-CC=NCH₃ has little effect.

The mixture of monosulfides 51 and 52 was heated with ethanol in an attempt to form the epimonothiodiketopiperazine 41 (n = 1). Only in a sealed tube at 125° did a reaction occur yielding, besides starting material, a compound with a slightly higher R₇ value on tlc. The compound had nearly the same mass spectrum as the starting mixture, with differences only in peak intensities, indicative of closely related isomers of 51 and/or 52. The nmr spectrum could best be interpreted as a mixture of structures 55 and 56 (Chart IX), compounds derived from the starting material by an interesting translactamization.

The two signals assigned to the N-methyl groups were shifted downfield (δ 3.23 and 3.13) and show a larger difference in chemical shifts than in 51 and 52 (Δδ = 5 and 2 Hz, respectively). Surprisingly only one broad signal was observable for the C₂' proton. Therefore, the possibility that we had in hand only one pair of enantiomers, 55 or 56, had also to be considered; the two signals for the N-methyl group could be explained by a conformational or long-range coupling effect.

However, nmr spectra at −20 or −40° and irradiation of the C₂' proton failed to change the relative intensities of the two N-methyl signals and indicated that the isolated material was most likely a mixture of two pairs of enantiomers, 55 and 56. An nmr of the recovered starting material mixture indicated that the proportion of 52 in the mixture had increased greatly and was now twice that of 51.

Particular attention was given to these considerations, for if only one pair of enantiomers had been formed, this probably would have been 55, derived only from the reactive starting material 51, via the desired diketopiperazine 41 (pathway A, Chart IX). A Dreiding model shows that the epimonothiodiketopiperazine ring system in 41 is a highly strained though not an impossible one as has been shown by Taylor. The occurrence of two pairs of enantiomers could then be explained by epimerization at C₂' in 55. A deuterium-exchange study is planned to check this possibility.

The occurrence of 55 and 56 would also be explained by pathway B, Chart IX. If the amide groups in 51 and 52 were cleaved by ethanol, the α-thio-bridged α-amino acid esters 53 and 54 would result. These could lactamize in two ways, yielding besides the starting materials the structures 55 and 56, respectively. Structures 53 and 54 with an unacylated α-thio amino acid moiety are undoubtedly unstable (see also Chart V and accompanying text), and should break down to the indolenine ester 17. However, the reaction mixture 51 + 52 ⇄ 55 + 56 showed only two spots on tlc with no trace of side products, making this mechanism unlikely.

Milder reaction temperatures and the use of non-protic solvents provided no new information. At 90° the formation of the new isomers is very slow and no new component could be detected; diglyme as solvent at 90 or 120° failed to give any identifiable product. At present there is no evidence permitting a choice between pathways A and B.

**Experimental Section**

Infrared spectra were measured with Perkin-Elmer spectrophotometers, Models 237B (CHCl₃ or CCl₄) and 421 (KBr), and uv spectra with a Cary Model 11 (95% EtOH). Mass spectra were obtained with the double-focusing Hitachi RMU-6E mass spectrometer. Proton magnetic resonance spectra were measured on the Varian Associates Model A-60 spectrometer. Chemical shifts are reported as δ values (ppm) relative to tetramethylsilane as an internal standard; deuteriochloroform was used as solvent unless stated.

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(46) Pojer and Rae described the synthesis of 13 and 2,2'-dibenzyldiketopiperazine in which the amino function is acetylated. Interestingly, the deacylated products were not mentioned.

(47) A Plancher rearrangement producing 57 and 58 cannot be completely ruled out. The shift in amide carbonyl absorption from 1690 to 1640 cm⁻¹ which accompanies this reaction is somewhat unexpected. Although the latter absorption is normal for a tertiary amide, it could also indicate that the amide is part of a six-membered ring. Arguing against this possibility, however, is the similarity of the 3'-methyl signals in the nmr spectra of starting materials and products.
otherwise. Melting points were taken on a Koller hot stage and are
accepted. Thin layer chromatography (tlc) was carried out using Merck precoated silica F-254 plates (thickness: 0.25 mm for analytical, 2.0 mm for preparative); spots were visualized with a uv hand lamp, iodine vapor, or a 0.1% solution of ninhydrin in methanol–1-butanol–2 N acetic acid (20:10:1 v/v).

Ethyl α-isopropylacetacetate (22). This compound was prepared from ethyl acetoacetate and 2-bromopropane following the procedure for the synthesis of ethyl n-propylacetacetate. 46 Vacuum distillation (34 mm) on a Viguex column yielded two fractions, bp 83–105° and 105–108°, the latter being the desired compound, the former being the O-alkylated product. 46 When freshly distilled ethyl acetoacetate was used, only the second, bp 22 resulted in 40% yield: nmr δ 1.4 (q, 2 H, CH₂(CH₃)₂), 3.22 (d, 1 H, COCHCO, J = 9 Hz), 2.40 (mult, 1 H, CH₂(CH₃)₂), 2.15 (s, 3 H, COCH₃), 1.21 (t, 3 H, CH₂CH₃), 0.9 (2 d, 6 H, CH₂CH₃CH₂CH₃, J = 6 Hz, spacing 2 Hz), O-Alkylated product: δ 4.14 (q, 2 H, CH₂), 3.45 (s, 1 H, COCCH₃) CH₂, 2.18 (s, 3 H, CH₃COCCH₃), 1.21 (t, 3 H, CH₃CH₂CH₃), 0.90 (2 d, 6 H, CH₂CH₃CH₂CH₃), J = 6 Hz, spacing 2 Hz).

Ethyl α-phenylacetylacetacetate (23). Solution A. A solution of 51.0 g (0.3 mol) of ethyl acetylacetacetate (22) in 200 ml of ethanol was cooled to −15° (ice-salt bath). Just before the addition of solution B to A, 232.5 ml of 5 N NaOH (1.15 mol), cooled to −15°, was added at once.

Solution B. A solution of potassiumodiazonium chloride was prepared from 27.9 g (0.30 mol) of freshly distilled aniline, 255 ml of 51.0 g (0.30 mol) of ethyl isopropylacetoacetate (22) in 5 N HCl, this oil was extracted with ether after acidification with 5% NaHC0₃ and filtered, and the ether was removed to yield a dark red residue. From this oil, 16.7 g (0.098 mol) of unreacted 22 could be isolated by vacuum distillation (bp 48–52° (0.5 mm)). The dark red residue (48.0 g, mp 100.5–101.5°) was crystallized from petroleum ether (80–100°) and the ether removed to yield 10.4 g (48 mmol, 94%) of a dark brown solid, which was purified by vacuum sublimation at 90° (1.0 mm), followed by recrystallization from petroleum ether (80–100°) at −20°. Large colorless needles with mp 78–79° (lit. mp 78–80°) were obtained (87% yield); tlc (5% ethanol–benzene) one spot; uv XmaxR⁢orio 294 and 232 nm (equal intensities); ir (KBr) 3070, 2980, 2980, 2870, 1713 (CO), 1542, 1460, 1365, 1310, 1280, 1210, 1190, 1120, 1090, 1065, 1050, 860, 785, 770, and 750 cm⁻¹; nmr δ 7.8 (mult, 1 H, C=CH), 7.35 (mult, 3 H, C₃H₆), 4.46 (2 H, CH₂CH₃), 1.52 (s, 6 H, CH₃CH₂CH₂CH₃), 1.43 (t, 3 H, CH₃CH₂), mass spectrum (31) M+ 217 (M+ – CH₃), 171 (M⁺ – OCH₃), 158, 145, 144 (M⁺ – CO₂CH₃), 143, 130, 128, 117, 115, 103, 91, 77. The ester 17 was also prepared according to Robinson and Sugi­nome. 41 from the hydrazone acid 25, yielding 6.5% of the ester 17 and 35.5% of the acid 26. The 20.2 g sample of the azo ester 23 was converted into 17 in 48% yield by the treatment given to the hydrazone ester 24 mentioned above. Both procedures led to material which was found to be identical in all respects with the specimen previously obtained.

Ethyl 1-Acetyl-2-thioacetyl-3,3-dimethylindoline-2-carboxylate and Isomer (28 and 29). A solution of 17 (343 mg, 2 mmol) in 4 ml of acetic acid distilled acetyl chloride was kept at 40° for 15 hr, during which time the reaction was monitored by tlc (5% ethanol–benzene). After addition of 5 ml of benzene, solvent and excess reagent were removed under vacuum and exclusion of moisture. Tlc (4% ethanol–benzene) showed two spots with Rf values smaller than the starting material: ir (CHC⁴H₄) 1790, 1690 cm⁻¹, disappearance of 1713 cm⁻¹; uv (CHC⁴H₄) values: 3.02 and 2800 cm⁻¹ (equal intensity of the ether 31). To the light brown oil was added an alcoholic solution of 570 mg of potassium thiocacetate after which potassium chloride separated. Stirring was continued for 2 hr; the alcohol was removed and the residue extracted with ether. The other layer was washed with 5% NaHCO₃ and water until neutral and dried (Na₂SO₄), and the ether was removed to yield 558 mg of the acid chloride 21 (6% ethanol–benzene) besides starting material, two spots with lower Rf. The oil was chromatographed on a silica gel column (100 g) with 4% ethanol–benzene, yielding three fractions: the first fraction appeared to be starting material 17 (30 mg), the second and third were assigned structures 29 and 28, respectively, on the following basis. Ir, identical for both fractions (CHC⁴H₄), 1790 (broad ester) and 1680 cm⁻¹ (broad, CON + COS). Fraction 2: nmr 8.7–7.0 (mult, 4 H, CH₂), 4.30 (2 H, CH₂CH₃), 2.48 (s, 3 H, CH₂CO), 2.32 (s, 3 H, CH₂CO), 1.47 (3 H, CH₃CH₂), 1.37 (s, 3 H, CH₃CH₂), 1.20 (3 H, CH₂CO), mass spectrum (190°) m/z 335 (M⁺), 305 (M⁺ – CH₃), 293 (CHₑCO), 260 (M⁺ – 217 (M⁺ – CO₂CH₃), 217 (M⁺ – OCH₃), 202 (M⁺ – CH₃, CH₂CO), 171 (M⁺ – OCH₃), 158, 145, 144 (M⁺ – CO₂CH₃), 143, 130, 128, 117, 115, 103, 91, 77. To the light brown oil was added with stirring an alcoholic solution of 40 mg of potassium thiocyanate after which potassium chloride separated. Stirring was continued for 15 min, the solvent removed, and the residue extracted with water–ether. The ether layer was washed twice with water and dried (Na₂SO₄), and the solvent was removed to yield 12 mg of a yellow oil: tlc (4% ethanol–benzene) showed only one spot, Rf 0.45; ir (CHC⁴H₄) 2980 (broad), 2040 (strong, broad, NH), 1760 (ester), 1680 cm⁻¹ (CH₂CON), mass spectrum (150°) m/z 318 (M⁺), 305, 278, 260 (M⁺ – NCS). 42, 234, 232, 217. Ethyl 1-Acetyl-2-thioacetyl-3,3-dimethylindoline-2-carboxylate (31). This compound was prepared according to Robinson and Sugiy­nome: 4.30 mmol of compound 21 and 3.4 g (43 mmol) of acetyl chloride was prepared as described above for the preparation of 30. To the light brown oil was added 5 ml of absolute ethanol; the solution was stirred for 2 hr at room temperature after which excess reagent was removed, yielding 470 mg of a yellow oil: tlc (4% ethanol–benzene) showed only one spot, Rf 0.20; nmr δ 7.8 (mult, 1 H, C=CH), 7.4–7.0 (mult, 3 H, C₃H₆), 4.30


(q, 2 H, COOCH3); 3.30 (q, 2 H, COCH2-), 2.35 (3 H, CH3CON), 1.45 (6, 6 H, CH2CH2); 1.32 (3 H, -COOCH3CH3); mass spectrum (160°) m/e 305 (M+), 275 (M+ - CH3), 232 (275 - CH2CO), 218, 217, etc.

2,9-Bis(4-oxopentyl)acetamide (33). The addition product of 17 (43 mg, 0.2 mmol) and 3.3 g (26 mmol) of N,N-dimethylacetamide benzene was prepared as described for the preparation of 30 (stirred for 15 hr). To the light yellow oil was added under stirring a solution of 381 mg (5 mmol) of thiourea in 10 ml of 2-propanol. Stirring was continued for 15 min, after which the clear solution was refluxed for 1 hr. Within a few minutes a precipitate formed. The reaction mixture was then cooled in ice, the precipitate filtered off, and from the filtrate the solvent was removed to yield 950 mg of a yellow powder: UV λmax EsHOT 247 nm (shoulders at 278 and 286 nm); pKb = 7.7; mnr 5.76 (1 H, C-H), 7.48 (mult, 3 H, C6-CH3), 4.44 (q, 2 H, CH2CH3), 3.31 (3 H, -COOCH3); 1.50 (3 H, 6 H, CH2CH2); 1.42 (3 H, -CH2CH3).

Conversion of 33 into 17. The yellow powder (100 mg) was dissolved in 10% of 40% ethanol; the pH of this solution was adjusted at 5.2 or in another experiment to 9.5 with 0.5 M NaHCO3, respectively. The reaction mixtures were refluxed for 5 min, then the volume was reduced to 5 ml, and the mixtures were extracted with ethyl acetate. The organic layers were dried (Na2SO4) and the solvents were removed, yielding 27 mg and 28 mg (59% and 60%, respectively) of crystalline material having Rf values, uv, and ir spectra identical with those of 17.

2-Carbethoxy-3,3-dimethylindolin-2-one (3,5 and 42). The addition product of 32 of 1.085 g (5 mmol) of 17 and 6.0 g of NaN3 (0.7 mol) was prepared analogous to the preparation of NaN3 from 10.2 g (0.33 mol) of powdered sulfur and 26 g (0.11 mol) of NaN3. Reaction conditions and work-up were the same as described above. After preparative tlc, 42 mg (14%) of 37 and 154 mg (47%) of 38 could be isolated besides 26 mg (12%) of the starting material 17.

Conversion of 38 into Monosulfide 37. A solution of 13 mg (4.1 × 10−4 mol) of 32 and 22 mg (8.4 × 10−4 mol) of triphenylphosphine in 1 ml of absolute ethanol was kept, wrapped in aluminum foil, at room temperature for 20 days. The rate of reaction was monitored by tlc. The solvent was removed and the residue subjected to preparative tlc (developed two times, 3% ethanol benzene), to yield 9.5 mg (3.25 × 10−4 mol, 80%) of 37. Identical by uv, ir (CHC13), and mass spectrum (180°). N-Trifluoracetyl-3,5-dichloroarsencarboxylic Acid Chloride (44). The synthesis of this compound (bp 54–58° (40 mm)) is described elsewhere.

2-Carbethoxy-3,3-dimethyl-9-methylleminindolin-2-one (3,5 and 42). The addition product of 1.52 g (7 mmol) of 17 and 3.8 g (14 mmol) of 44 in 25 ml of dry benzene was prepared as described for the preparation of 38. The reaction mixture was stirred for 15 hr and yielded 3.86 g of a light yellow oil. To an ice-cold solution of this oil in 30 ml of dry diglyme was added quickly an ice-cold, freshly prepared aqueous solution of sodium tetrafluoroborate (40 ml, 44 mmol, prepared as described for the synthesis of 37 and 38). The reaction mixture was kept at 0° and stirred for 5 min, after which it was extracted withethyl acetate. The layer was washed with water (2 × 50 ml) and stirred for 5 min. The solvent was removed to yield 1.94 g of a dark brown oil: 0.65 g of this oil was subjected to preparative tlc on five plates (developed two times with 4% ethanol-benzene) to yield 192 mg (88%, 38%) of starting material and 270 mg of a still impure, ninhydrin-positive material. The latter was recrystallized on five plates as before yielding 320 mg (0.7 mmol, 30%) of crystalline material (ninhydrin-positive) which could be further purified by vacuum sublimation at 100° (0.5 mm): tlc (5% ethanol-benzene), one spot Rf 0.41. A small sample was crystallized from slowly evaporating chloroform: mp 101–102°; ir (CHC13) 1745, 1455, 1390, and 1290 cm−1; nmr δ 7.88 (mult, 1 H, C2-H), 7.22 (mult, 3 H, C6-CH3), 4.15 (q, 2 H, CH2CH3), 3.00 (m, 1 H, C2CH3), 2.71 (t, 3 H, CH3), 1.18 (3 H, 3 H, CH3); mass spectrum (160°), m/e 318 (M+). 324 (M+ - CH3), 274 (M+ - OCH3), 259 (274 - CH3), 245 (M+ - COCH3, base peak), 230 (245 - CH3), 218, 204, 202, etc.

2-Carbethoxy-3,5-dimethyl-9-methylaminoindolin-2-one (3,5 and 42). To a solution of 285 mg (0.9 mmol) of the Schiff's base in 5 ml of absolute ethanol at room temperature was added a trace of bromocresol green; 2 N methanolic HCl was added until the indicator turned yellow, and 200 mg (3.2 mmol) of sodium cyanoborohydride was added with stirring. Additional HCl-methanol solution was added to maintain the yellow color. Stirring was continued for 10 min. The solution was poured into 50 ml of ice-cold 0.1 N NaOH, saturated with NaCl and extracted twice with ice-cold ethyl acetate. The combined organic layers were dried (Na2SO4) and concentrated in vacuo to give 288 mg (0.8 mmol, 100%) of a colorless oil, which showed only one spot on tlc (5% ethanol-benzene, Rf 0.38, ninhydrin-positive): ir (CHC13) 3350 (weak, broad, NH), 2940, 2930, 2870, 1705 (ester), 1635 (amide), 1500, 1490, 1480, 1460, 1395, 1370, 1290, and 1265 cm−1; nmr δ 7.81 (1 H, C2-H), 7.21 (mult, 3 H, C6-CH3), 1.49, 1.34, and 1.25 (overlapping singlets, 3 H, CH3); mass spectrum (160°), m/e 320 (M+), 279 (M+ - CH3), 274 (M+ - COCH3), 265, 247, 234, 230, 219, 218, 202, 192, 178, 175, 149, 146 (base peak).

Rearrangement of 51 into 55 and 56. A solution of 40 mg (0.126)

(50) According to IUPAC rules the nomenclature for 37 and 38 should be 2,3,9,9a-tetrahydro-3-keto-9,9-diethyl-9a-carbethoxythiazolo[3,2-d]indole and 3,4,5,6,10a-hexahydro-4-keto-10,10-dimethyl-10a-carbethoxy-2,5-dihydrothiazolo[5,6-d]indole, respectively. For convenience we use the names above.

mmol) of the mixture of $51$ and $52$ in 5 ml of absolute ethanol was heated in a sealed ampoule at 108° for 24 hr and then at 125° for 16 hr. Tlc (6% ethanol–benzene) showed the presence of only two products, the starting material and a product with larger $R_t$. The solvent was removed and the brown oily residue subjected to preparative tlc (developed three times with 5% ethanol–benzene), to yield 26 mg (65%) of "starting material" and 14 mg (35%) of isomerized product: tlc (6% ethanol–benzene) only one spot, $R_t$ 0.50; ir (CHCl$_3$) 3400 (sharp, NH), 2980, 2940, 2860, 1730 (ester), 1640 (amide), 1600, 1525, 1480, 1460, 1395, and 1370 cm$^{-1}$; nmr $\delta$ 8.15 (mult, 1 H, C$_7$–H), 7.20 (mult, 3 H, C$_4$–H), 5.50 (broad singlet, 1 H, C$_5$–H), 4.17 (q, 2 H, CH$_2$CH$_3$), 3.23 and 3.13 (2 singlets, separated 5 Hz, 3 H, N–CH$_3$), 2.0 (broad s, 1 H, NH), 1.47 and 1.29 (2 singlets, 6 H, CH$_3$CH$_2$), 1.29 (t, 3 H, CH$_3$CH$_2$); mass spectrum (160°), $m/e$ 320 (M$^+$), identical with that for $51$ and $52$, except for a stronger signal at $m/e$ 304 (M$^+$ – CH$_4$) and a weaker one at $m/e$ 247 (M$^+$ – CO$_2$C$_2$H$_5$) and 245.

The nmr spectrum of the isolated "starting material" showed a change in that the ratio of the two signals from the C$_7$-proton was reversed (now $\delta$ 5.65/5.29 = 1:2), indicating that only the cis enantiomers $51$ have been isomerized.

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