Synthesis of Novel Indolizine Derivatives

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The reaction of a number of γ-butyrolactones with azole anions is shown to give γ-substituted butanoic acids in moderate to good yields. The pyrrolyl and indolylbutanoic acids obtained underwent cyclization in a simple one-pot procedure employing ethyl chloroformate and boron trifluoride etherate. Some aspects of the chemistry of the resulting indolizin-8-ones are described.

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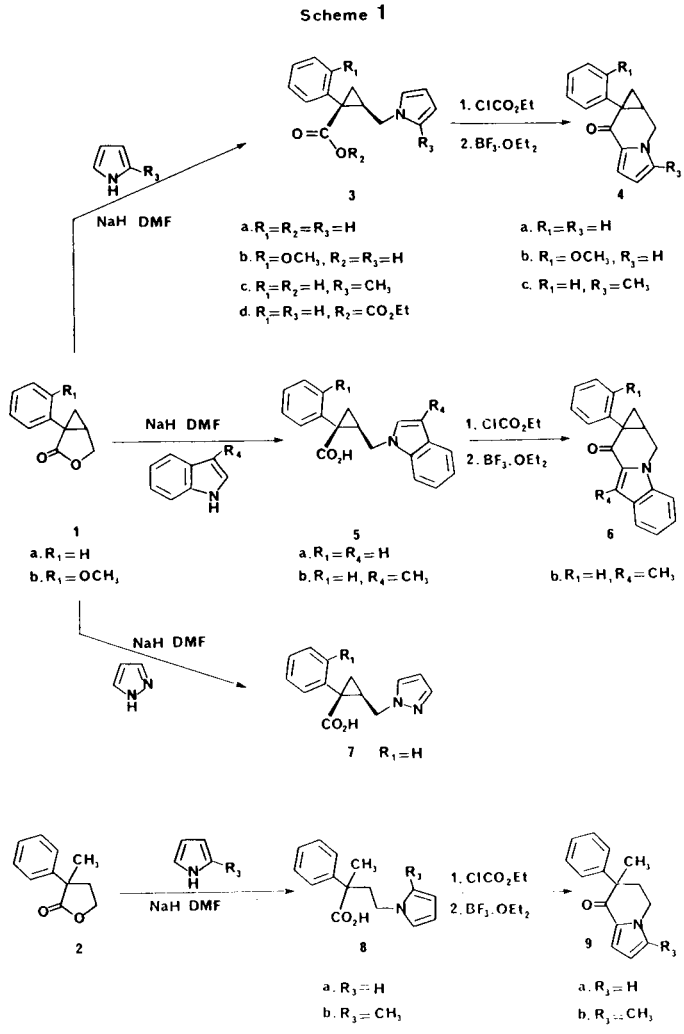
For several years we have been involved in the synthesis of cyclopropane derivatives and their pharmacological evaluation, in particular as analgesics [1] and antidepressants [2]. In continuation of this work based on the chemistry of bicyclic lactones [3-6] our interest has lately been directed towards the synthesis of new cyclopropa[6,7]indolizines and related compounds. We now describe the ring-opening reactions of a number of γ-butyrolactones with azole anions and the cyclization of the resulting acids. The chemistry of the indolizin-8-ones obtained has been briefly investigated.

Scheme 1



The ring-opening reactions of γ-butyrolactones with nucleophiles such as phenols and thiophenols [7-10], phthalimide [11,12], and lactams [13,14] are well known. In contrast, the reaction of γ-butyrolactones with azole anions has received little attention [15] although such reactions are of mechanistic interest since both partners may show ambident character.

As shown in Scheme 1 pyrrolyl anions reacted with lactones **1a**, **1b** at the soft sp^3 carbon atom to afford acids **3a**, **3b** and **3c** in good yield under conditions which favour *N*-alkylation [16,17] (deprotonation with sodium hydride in a solvent of high dielectric constant). Analogous reactions with the unstrained lactone **2** led to compounds **8a** and **8b**, albeit in somewhat lower yield. Pyrazolyl and indolyl anions similary gave *N*-alkylated products **5** and **7** with lactone **1**. No reaction was, however, observed between lactone **1** and the anion derived from imidazole.

The cyclization of acid **3a** was examined using a variety of methods described for related heterocyclic systems [18-25]. Heating acid **3a** in ethanolic sulfuric acid at reflux failed to effect cyclization, and led to formation of the ester **10**, while use of trifluoroacetic anhydride gave the acylated pyrrole **11** (Scheme 2). Treatment of **3a** with polyphosphoric acid at 80° afforded the expected ketone **4a**, but in moderate yield. Cyclization reactions *via* activated acid derivatives gave variable results as shown in Table 1.

Scheme 2

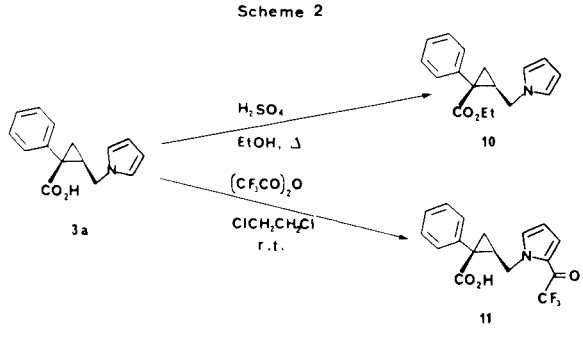


Table 1

Ring Closure Reactions of 3a

Experimental Conditions	Product	Yield (%)
H_2SO_4 (concentrated), Ethanol, Reflux 8 hours	10	75
$(CF_3CO)_2O$, $ClCH_2HC_2Cl$, 25°, 1 hour	11	68
Polyphosphoric acid, 80°, 3 hours	4a	43
$SOCl_2$, $ClCH_2CH_2Cl$, Reflux 1 hour/$AlCl_3$, 25°, 1 hours	[a]	
ClCOCOCl, 25°, 2 hours/$AlCl_3$, 25°, 15 hours	[a]	
$ClCOOC_2H_5$, TEA, 0°/CF_3COOH, 25°, 15 hours	4a	24
$ClCOOC_2H_5$, TEA, 0°/$AlCl_3$, 25°, 15 hours	4a	30
$ClCOOC_2H_5$, TEA, 0°/$BF_3 \cdot OEt_2$, 25°, 15 hours	4a	72

[a] Intractable tars.

Optimal results were obtained by activation of the acid with ethyl chloroformate followed by boron trifluoride etherate induced cyclization. The intermediate **3d** is a stable crystalline solid which was characterized. Its isolation is not, however, necessary since a one-pot method gives comparable results. This mild cyclization procedure may be of more general utility since the cyclopropyl pyrroles **3b** and **3c** and the open-chain compounds **8a** and **8b** were readily cyclized in a similar fashion to afford **4b**, **4c**, **9a** and **9b** respectively. Cyclization of the indole derivative **5b** gave **6b** in an analogous fashion, but attempted cyclization of **5a** gave intractable tars and the pyrazole **7**, not unexpectedly, failed to undergo cyclization under these conditions [26].

The chemistry of the 3'H-cyclopropa[6,7]-5,6,7,8-tetra-

Scheme 3

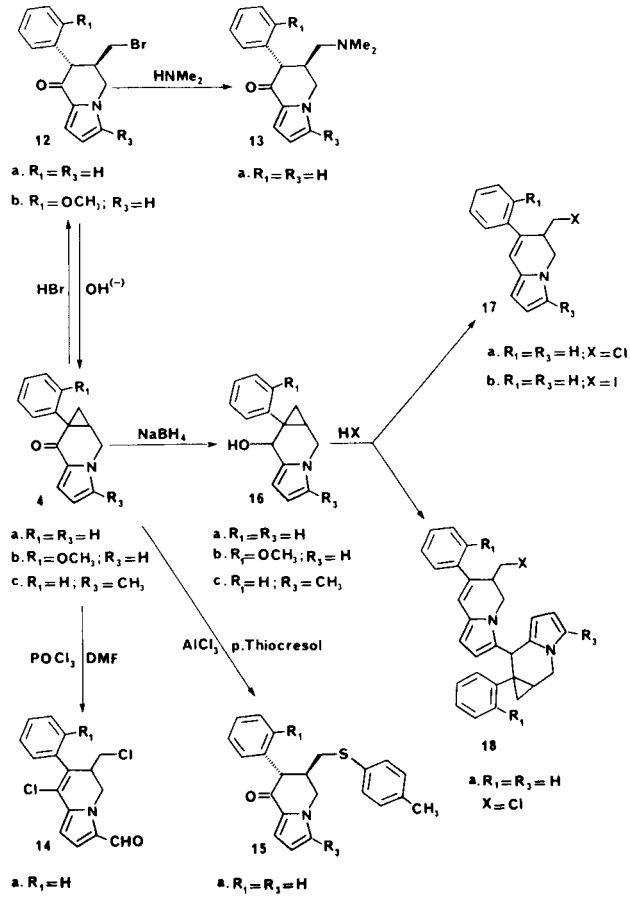


Table 2

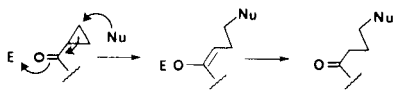
Analytical and Spectral Data of Carboxylic Acids 3, 5, 7, 8

Compound No.	Yield (%)	mp (°C)	Formula	Analysis Calcd./Found C	H	N	IR (C=O) (cm^{-1})	^1H NMR (deuteriochloroform) (ppm)
3a	75	176-178	$C_{15}H_{15}NO_2$	74.67 74.50	6.27 6.26	5.81 5.78	1675	1.33 (dd, 1H), 1.77 (m, 2H), 4.10 (d, 2H), 5.87 (t, 2H), 6.53 (t, 2H), 7.00 (s, 5H)
3b	65	175-177	$C_{16}H_{17}NO_3$	70.83 70.39	6.32 6.26	5.16 5.11	1665	1.42 (dd, 1H), 1.61 (dd, 1H), 2.03 (m, 1H), 3.77 (s, 3H), 4.32 (d, 2H), 6.19 (t, 2H), 6.75 (t, 2H), 6.65 (t, 2H), 7.07 (d, 1H), 7.27 (dt, 1H)
3c	66	154-156	$C_{16}H_{17}NO_2$	75.27 75.28	6.71 6.81	5.49 5.55	1680	1.56 (m, 1H), 1.64 (m, 1H), 1.96 (m, 1H), 2.30 (s, 3H), 4.23 (d, 2H), 5.94 (d, 1H), 6.12 (d, 1H), 6.67 (s, 1H), 7.27 (m, 5H)
5a	51	124-126	$C_{19}H_{17}NO_2$	78.33 78.26	5.88 5.93	4.81 4.87	1670	1.59 (m, 1H), 1.92 (m, 1H), 2.22 (m, 1H), 5.60 (m, 2H), 6.58 (d, 1H), 7.19-7.42 (m, 9H), 7.69 (d, 1H)
5b	42	134-136	$C_{20}H_{19}NO_2$	78.66 78.27	6.27 6.27	4.59 4.59	1675	1.56 (dd, 1H), 1.91 (t, 1H), 2.16 (m, 1H), 2.36 (s, 3H), 4.50 (d, 2H), 6.94 (s, 1H), 7.20 (m, 8H), 7.60 (d, 1H),
7	43	164-166	$C_{14}H_{14}N_2O_2$	69.40 69.80	5.82 5.76	11.56 11.50	1680	1.45 (dd, 1H), 1.76 (dd, 1H), 2.12 (m, 1H), 4.44-4.60 (m, 2H), 6.32 (t, 1H), 7.20 (m, 5H), 7.57 (d, 2H)
8a	53	126-128	$C_{15}H_{17}NO_2$	74.05 73.42	7.04 7.06	5.76 5.80	1695	1.68 (s, 3H), 2.48 (m, 2H), 3.63 (t, 2H), 6.14 (t, 2H), 6.62 (t, 2H), 7.35 (m, 5H)
8b	39	123-125	$C_{16}H_{19}NO_2$	74.68 74.72	7.44 7.37	5.44 5.51	1690	1.71 (s, 3H), 2.14 (s, 3H), 2.28-2.45 (m, 2H), 3.69-3.77 (m, 2H), 5.85 (t, 1H), 6.03 (q, 1H), 6.51 (q, 1H), 7.36 (m, 5H)

Table 3
Analytical and Spectral Data of Ketones 4, 6, 9

Compound No.	Yield (%)	mp (°C)	Formula	Analysis Calcd./Found C	H	N	IR (C=O) (cm^{-1})	^1H NMR (deuteriochloroform) (ppm)
4a	72	156-158	$C_{15}H_{13}NO$	80.69 80.94	5.87 5.83	6.27 6.32	1630	1.42 (dd, 1H), 1.74 (dd, 1H), 2.20 (m, 1H), 4.52 (m, 2H), 6.30 (dd, 1H), 6.80 (t, 1H), 6.97 (dd, 1H), 7.32 (m, 5H)
4b	58	149-151	$C_{16}H_{15}NO_2$	75.87 75.98	5.97 6.05	5.53 5.54	1635	1.36 (m, 1H), 1.76 (m, 1H), 1.90 (m, 1H), 3.79 (s, 3H), 4.51 (m, 2H), 6.28 (q, 1H), 6.79 (t, 1H), 6.88-7.00 (m, 3H), 7.29 (m, 2H)
4c	55	189-191	$C_{16}H_{15}NO$	80.98 80.41	6.37 6.45	5.90 5.92	1645	1.38 (t, 1H), 1.72 (dd. 1H), 2.20 (m, 1H), 2.29 (s, 3H), 4.25 (dd, 1H), 4.44 (dd, 1H), 6.07 (d, 1H), 6.95 (d, 1H), 7.33 (m, 5H)
6b	68	137-139	$C_{20}H_{17}NO$	83.59 83.71	5.96 5.99	4.88 5.00	1640	1.58 (t, 1H), 1.79 (dd, 1H), 2.35-2.43 (m, 1H), 2.65 (s, 3H), 4.41 (dd, 1H), 4.78 (dd, 1H), 7.26 (m, 1H), 7.40 (m, 7H), 7.42 (d, 1H)
9a	70	oil	$C_{15}H_{15}NO$				1650	1.56 (s, 3H), 2.37-2.52 (m, 1H), 2.57-2.68 (m, 1H), 3.66-3.75 (m, 1H), 3.99-4.09 (m, 1H), 6.26 (m, 1H), 6.75 (m, 1H), 7.13 (m, 1H), 7.22 (m, 5H),
9b	58	oil	$C_{16}H_{17}NO$				1640	1.57 (s, 3H), 2.16 (s, 3H), 2.36-2.49 (m, 1H), 2.59-2.70 (m, 1H), 3.50-3.64 (m, 1H), 3.86-3.96 (m, 1H), 6.04 (m, 1H), 7.09 (m, 1H), 7.27 (m, 5H),

hydroindolizin-8-ones obtained is of interest since the pyrrole ring is reactive towards electrophiles, while nucleophiles may attack either the carbonyl group or the cyclopropyl ring, the latter site being favoured under "push-pull" conditions. [27].



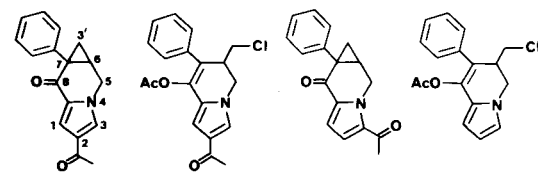
Thus ketones **4a** and **4b** on treatment with a 33% solution of hydrobromic acid in acetic acid at room temperature gave the bromoketones **12a** and **12b** respectively in high yield (Scheme 3), and the use of a *p*-thiocresol/aluminum chloride combination led to derivative **15a**. In the latter case the ring-opening reaction is not regioselective and the isomeric seven-membered ring is also obtained.

Reaction of the bromoketone **12a** with dimethylamine gave **13a**, but the use of other secondary amines or potassium phthalimide led to reformation of the cyclopropyl ketone **4a**.

Under Vilsmeier conditions the ketone **4a** underwent multiple reactions leading to **14a** illustrating the nucleophilic and electrophilic properties of the molecule. Reduction of **4a**, **4b**, and **4c** with sodium borohydride gave the acid-labile alcohols **16a**, **16b** and **16c**.

Treatment of **16a** with hydriodic acid gave **17b** while hydrochloric acid treatment led to a mixture of the homoallylic chloride **17a** along with the dimeric product **18a**.

Acylation of **4a** was studied with acetic anhydride and acetyl chloride in the presence of aluminum chloride and boron trifluoride etherate. As shown in Table 4 acylation at the 2-position of the indolizine predominates under most conditions, and is exclusive with aluminum chloride as catalyst. Although the acylations are complicated by ring-opening reactions, compound **20** may be obtained in 80% yield by base treatment of the reaction mixture obtained by the acetic anhydride/aluminum trichloride method (entry 2).



20 **21** **22** **23**

Table 4
Results of Acylation of Ketone 4a

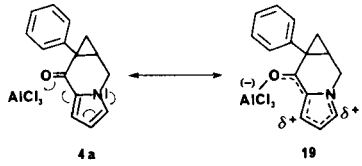
Entry	Experimental Conditions	Compounds (% isolated) 20	21	22	23
1	Ac_2O, $BF_3 \cdot OEt_2$, CH_2Cl_2, 25°, 15 hours	44		10	
2	Ac_2O, $AlCl_3$, CH_2Cl_2, 25°, 15 hours	56	30		
3	CH_3COCl, $BF_3 \cdot OEt_2$, CH_2Cl_2, 25°, 15 hours	trace			
4	CH_3COCl, $AlCl_3$, CH_2Cl_2, 25°, 15 hours	35	27	trace	14

Table 5

Analytical and Spectral Data of Compounds Obtained from Ketones 4a,b,c

Compound No.	mp (°C)	Yield (%)	Formula	Analysis Calcd./Found C	H	N	Br	Cl	IR (C=O) (cm^{-1})	^1H NMR (deuteriochloroform) (ppm)
12a	143-145	86	$C_{15}H_{14}BrNO$	59.23	4.64	4.60	26.27		1650	2.87 (m, 1H), 3.18 (dd, 1H), 3.41 (dd, 1H), 3.74 (d, 1H), 4.18 (dd, 1H), 4.38 (dd, 1H), 6.33 (dd, 1H), 6.91 (t, 1H), 7.08-7.40 (m, 6H)
				59.14	4.62	4.65	25.95			
12b	149-151	75	$C_{16}H_{16}BrNO_2$	57.50	4.82	4.19	23.90		1645	3.20 (m, 2H), 3.40 (dd, 1H), 3.73 (s, 3H), 3.83 (d, 1H), 4.18 (dd, 1H), 4.38 (dd, 1H), 6.31 (m, 1H), 6.91-7.35 (m, 6H)
				57.63	4.87	4.33	24.09			
16a	104-106	76	$C_{15}H_{15}NO$	79.97	6.71	6.22				0.74 (t, 1H), 1.06 (m, 1H), 1.69 (m, 1H), 1.90 (d, 1H), 4.30 (d, 2H), 5.29 (d, 1H), 6.22 (m, 2H), 6.60 (t, 1H), 7.30-7.47 (m, 5H)
				79.73	6.75	6.27				
16b	101-103	68	$C_{16}H_{17}NO_2$	75.27	6.71	5.49				0.69 (t, 1H), 0.95 (m, 1H), 1.56 (m, 1H), 2.06 (d, 1H), 3.67 (s, 3H), 4.31 (m, 2H), 5.21 (d, 1H), 6.19 (t, 2H), 6.60 (t, 1H), 6.95 (m, 2H), 7.30 (m, 2H)
				75.57	6.71	5.65				
16c	oil	83	$C_{16}H_{17}NO$							0.79 (t, 1H), 1.03 (m, 1H), 1.71 (m, 1H), 1.82 (d, 1H), 2.23 (s, 3H), 4.05 (dd, 1H), 4.25 (dd, 1H), 5.28 (d, 1H), 5.93 (d, 1H), 6.13 (d, 1H), 7.23-7.48 (m, 5H)
20	219-221	56	$C_{17}H_{15}NO_2$	76.96	5.70	5.28			1645	1.41 (t, 1H), 1.77 (dd, 1H), 2.27 (m, 1H), 2.43
				76.89	5.62	5.44			(broad)	(s, 3H), 4.57 (m, 2H), 7.26-7.37 (m, 7H)
21	120-122	30	$C_{19}H_{18}ClNO_3$	66.38	5.28	4.07		10.31	1760	2.10 (s, 3H), 2.41 (s, 3H), 3.24-3.42 (m, 2H),
				66.71	5.31	4.29		10.43	1640	3.57 (dd, 1H), 4.25 (dd, 1H), 4.53 (d, 1H), 6.55 (d, 1H), 7.26-7.36 (m, 6H)
22	170-172	10	$C_{17}H_{15}NO_2$	76.96	5.70	5.28			1640	1.40 (t, 1H), 1.77 (dd, 1H), 2.31 (m, 1H), 2.52
				76.73	5.62	5.37			(broad)	(s, 3H), 4.50 (dd, 1H), 5.48 (d, 1H), 6.93 (d, 1H), 6.98 (d, 1H), 7.33 (m, 5H)
23	146-148	14	$C_{17}H_{16}ClNO_2$	67.66	5.34	4.64		11.75	1750	2.10 (s, 3H), 3.25 (m, 1H), 3.37-3.61 (m, 2H),
				67.91	5.38	4.69		11.87	1640	4.18 (dd, 1H), 4.49 (dd, 1H), 6.16 (m, 2H), 6.76 (m, 1H), 7.30 (m, 5H)

The directing effect observed in the acylation of analogous pyrroles in the presence of an excess of aluminum chloride has been attributed [28] to the formation of a complex (**19** in our case) where a partial positive charge deactivates the α- and γ-positions reative to the β-position.



4a 19

EXPERIMENTAL

Melting points were determined using a Kofler block (Heizbank WME) and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 177 infrared spectrometer. The ^1H nmr spectra were recorded using a Bruker AC-200 spectrometer and chemical shifts (δ) are reported in ppm relative to tetramethylsilane. Ascending thin layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots visualized using a uv lamp or iodine vapor. E. Merck silica gel 60 F (70-230 mesh) was used for column chromatography. The elemental analyses were carried out using a Carlo Erba Model 1106 elemental analyzer. The starting lactone **2** was obtained by α-methylation of α-phenyl butyrolactone prepared according to a reported procedure [29].

General Procedure for the Preparation of γ-*N*-Heterocyclic Acids **3,5,7,8**.

To a stirred solution of heterocyclic amine (0.057 mole) in dimethylformamide (40 ml) under nitrogen was added portionwise sodium hydride (0.063 mole, 60% dispersion in mineral oil) at room temperature over a 30 minute period. After stirring one hour at 60° the lactone **1** or **2** was added and the reaction mixture was heated at 60° with stirring for 5 hours. The cooled solution was added to ice-water and a neutral fraction was extracted with ether. The aqueous phase was acidified with 6*N* hydrochloric acid and the resulting precipitate was filtered, washed with water and air dried. The crude product was recrystallized from diisopropyl ether (Table 2).

General Procedure for the Preparation of Heterocyclic Ketones **4,6,9**.

A solution of 20 ml of 1,2-dichloroethane containing acid **3**, **5**, or **8** (0.01 mole) and *N*-methylmorpholine (0.011 mole) was stirred in an ice-bath and treated dropwise with ethyl chloroformate (0.011 mole). The reaction mixture was stirred at room temperature for 2 hours, the *N*-methylmorpholine hydrochloride formed was filtered and washed with 1,2-dichloroethane. Boron trifluoride etherate (0.021 mole) was added at 0° to the mother liquor and the reaction mixture was stirred at room temperature overnight. The organic phase was washed twice with water and the

dried (sodium sulfate) organic extract was concentrated under reduced pressure. The crude product was purified by flash-chromatography using silica gel with chloroform as eluent followed by crystallization from diisopropyl ether (except ketones **9a** and **9b**, which were oils) (Table 3).

General Procedure for the Preparation of Cyclopropyl Alcohols **16a, b, c.**

A mixture of ketone **4a**, **4b** or **4c** (0.02 mole), polyethyleneglycol 400 (20 ml) and sodium borohydride (0.04 mole) was stirred at room temperature for 1 hour, then heated at 80° for 2 hours. The solution was cooled to room temperature and diluted with water. The crude alcohol was extracted twice with ethyl acetate and the extracts washed with water, dried (sodium sulfate) and filtered. The residual oil obtained after evaporation of the ethyl acetate was recrystallized from dichloromethane-diisopropyl ether (Table 5).

General Procedure for the Acylation of **4a.**

To the solution of **4a** (0.01 mole) in dichloromethane (10 ml), was added acetic anhydride or acetyl chloride (0.012 mole) with stirring and ice-bath cooling. The catalyst (boron trifluoride etherate or aluminum chloride) (0.03 mole) was then added in portions. The resulting mixture was allowed to warm to ambient temperature and stirring was continued for 15 hours. The reaction mixture was poured into ice-water and extracted with dichloromethane. The organic layer was washed successively with water, 5% aqueous sodium bicarbonate and water. After drying over sodium sulfate the dichloromethane was evaporated under reduced pressure and the residual oil was crystallized from ethyl acetate to give the acylated product **20**. The other products were isolated by chromatography of the mother liquor over silica gel using ethyl acetate:hexane (4:1) (Table 5).

In a repeated experiment in the case of entry 2 (Table 4) the crude oil dissolved in acetone was treated with an excess of concentrated sodium hydroxide solution. After 2 hours at room temperature the solution was concentrated under reduced pressure and the product precipitated by the addition of water. After filtration and drying the acylated derivative **20** was obtained (yield 80%).

General Procedure for the Preparation of Bromoketones **12a, b.**

The ketone **4a** or **4b** (0.01 mole), was added in portions with stirring and ice-bath cooling to 23 ml of a 33% solution of hydrobromic acid in acetic acid. The solution was stirred at room temperature for 15 hours then poured into ice-water. The solid was collected by filtration, dried *in vacuo* and recrystallized from ethyl acetate-diisopropylether to give the bromoketones **12a** and **12b** (Table 5).

cis-1-Phenyl-1-(ethoxycarbonyloxycarbonyl)-2-(1-pyrrolylmethyl)-cyclopropane **3d.**

A portion of the 1,2 dichloroethane solution of the mixed anhydride (see general procedure for the preparation of heterocyclic ketones) was washed with water, sodium bicarbonate solution and water. The organic phase was dried (sodium sulfate), filtered and the solvent was removed under reduced pressure. The analytical sample was obtained as a white solid *via* silica gel chromatography (chloroform) and crystallization from diisopropyl ether-hexane, mp 45-50° dec; ir (potassium bromide): 1795 and 1735 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.23 (t, 3H), 1.30-2.30 (m, 3H), 4.10 (q, 2H), 4.15 (d, 2H), 5.97 (t, 2H), 6.50 (t, 2H), 6.97 (s, 5H).

Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.18; H, 6.10; N, 4.53.

cis-Ethyl 1-Phenyl-2-(1-pyrrolylmethyl)cyclopropanecarboxylate **10.**

A mixture of 1.2 g (0.05 mole) of **4a**, 25 ml of ethanol and 1.25 ml of concentrated sulfuric acid was refluxed for 8 hours. The solution was concentrated under reduced pressure and poured into water. The mixture was extracted with ethyl acetate, washed with water, dried (sodium sulfate) and filtered. Ethyl acetate was removed under reduced pressure and the residual oil was crystallized from diisopropyl ether-hexane to give 1 g (75%) of **10**, mp 93-95°; ir (potassium bromide): 1700 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.05 (t, 3H), 1.30 (dd, 1H), 1.77 (m, 2H), 3.97 (q, 2H), 4.05 (d, 2H), 5.97 (t, 2H), 6.50 (t, 2H), 6.97 (s, 5H).

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.56; H, 7.08; N, 5.20.

cis-1-Phenyl-2[(2-trifluoroacetyl-1-pyrrolyl)methyl]cyclopropanecarboxylic Acid **11.**

To a suspension of 0.48 g (0.002 mole) of **4a** and 7 ml of 1,2-dichloroethane, was added 1.4 ml (0.01 mole) of trifluoroacetic anhydride. The solution was stirred at room temperature for 1 hour, then the mixture was concentrated under reduced pressure. The crude product was extracted with dichloromethane, washed with water, dried (sodium sulfate) and filtered. Dichloromethane was removed under reduced pressure and the residual oil was crystallized from diisopropyl ether-hexane to give 0.46 g (68%) of **11**, mp 118-120°; ir (potassium bromide): 1660 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.60 (dd, 1H), 1.70 (dd, 1H), 2.17 (m, 1H), 4.55 (d, 2H), 6.07 (dd, 1H), 6.97 (m, 7H).

Anal. Calcd. for $C_{17}H_{14}F_3NO_3$: C, 60.54; H, 4.18; N, 4.15. Found: C, 60.89; H, 4.30; N, 4.06.

trans-6-Dimethylaminomethyl-7-phenyl-5,6,7,8-tetrahydroindolizin-8-one **13a.**

A solution of a 3.04 g (0.01 mole) of **12a** and 30 ml of 33% ethanolic dimethylamine solution was kept in a closed vessel at 100° for 15 hours. The solvent was removed under reduced pressure and the residue was stirred with 25 ml of 1*N* hydrochloric acid. The crystalline product obtained was collected by filtration, washed with water and dried (ketone **4a**, 1 g, 45%). The aqueous filtrate was basified with concentrated sodium hydroxide and the precipitate collected by filtration, washed with water and dried. The product was recrystallized from ethanol to give 1.26 g (47%) of **13**, mp 170-172°; ir (potassium bromide): 1640 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 2.05 (dd, 1H), 2.17 (s, 6H), 2.35 (t, 1H), 2.73 (m, 1H), 3.54 (d, 1H), 3.96 (dd, 1H), 4.42 (dd, 1H), 6.32 (dd, 1H), 6.91 (d, 1H), 7.06-7.15 (m, 3H), 7.27-7.38 (m, 3H).

Anal. Calcd. for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.44. Found: C, 75.97; H, 7.45; N, 10.45.

3-Formyl-6-chloromethyl-7-phenyl-8-chloro-5,6-dihydroindolizine **14a.**

To 5 ml of dimethylformamide cooled in an ice-bath was added dropwise with stirring 1.37 ml of phosphorus oxychloride

(0.015 mole). The solution was allowed to warm to room temperature and 2.23 g (0.01 mole) of ketone **4a** in 10 ml of dimethylformamide was added dropwise. After stirring for 15 hours, the solution was poured into ice-water and basified with potassium carbonate. The resulting solid was collected by filtration, washed with water, and dried. Purification by column chromatography over silica gel using chloroform as eluent and recrystallization from diisopropyl ether yielded 1.7 g (55%) of **14a**, mp 120-122°; ir (potassium bromide): 1655 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 3.26 (m, 2H), 3.47 (m, 1H), 4.21 (dd, 1H), 5.60 (dd, 1H), 6.55 (d, 1H), 6.96 (d, 1H), 7.44 (m, 5H), 9.63 (s, 1H).

Anal. Calcd. for $C_{16}H_{13}Cl_2NO$: C, 62.76; H, 4.28; N, 4.57; Cl, 23.16. Found: C, 63.03; H, 4.36; N, 4.70; Cl, 23.43.

trans-6-[(4-Methylphenyl)thiomethyl]-7-phenyl-5,6,7,8-tetrahydroindolizin-8-one **15a**.

Aluminum chloride (1 g, 0.0075 mole) was added in portions with stirring to a solution of 1.12 g (0.005 mole) of **4a** in 15 ml of acetonitrile. A solution of 1.24 g (0.01 mole) of parathiocresol in 5 ml acetonitrile was added and the reaction mixture heated with stirring for 10 hours at 60°. The mixture was poured into water and extracted twice with ethyl acetate. The combined organic extracts were washed with 0.5 *N* aqueous sodium hydroxide, water, dried and filtered. Ethyl acetate was removed under reduced pressure. Purification over silica gel using hexane-ethyl acetate (85:15) as eluent followed by crystallization from diisopropyl ether gave 1 g (57%) of **15a**, mp 98-100°; ^1H nmr (deuteriochloroform): δ 2.32 (s, 3H), 2.62 (m, 2H), 3.05 (d, 1H), 3.67 (d, 1H), 4.04 (dd, 1H), 4.47 (dd, 1H), 6.31 (m, 1H), 6.67 (m, 1H), 7.10 (m, 7H), 7.31 (m, 3H).

Anal. Calcd. for $C_{22}H_{21}NOS$: C, 76.06; H, 6.09; N, 4.03; S, 9.22. Found: C, 76.32; H, 6.09; N, 4.23; S, 9.36.

6-Chloromethyl-7-phenyl-5,6-dihydroindolizine **17a** and Dimer **18a**.

To a solution of 6.08 g (0.027 mole) of **16a** in 50 ml of ethyl acetate was added dropwise 15 ml of 2.4 *N* hydrochloric acid ethyl acetate solution. After stirring for 15 minutes at room temperature, the solution was washed with 5% sodium bicarbonate, water, dried and filtered. Ethyl acetate was removed under reduced pressure and the crude product was submitted to chromatography over silica gel using ethyl acetate-hexane (85:15). Compound **17a** eluted first, yield 1 g (15%) (amorphous yellow solid); ^1H nmr (deuteriochloroform): δ 3.38 (m, 2H), 3.58 (dd, 1H), 4.03 (dd, 1H), 4.54 (d, 1H), 6.22 (d, 2H), 6.73 (t, 1H), 6.96 (s, 1H), 7.25-7.58 (m, 5H).

Anal. Calcd. for $C_{15}H_{14}ClN$: C, 73.92; H, 5.79; N, 5.75; Cl, 14.54. Found: C, 74.20; H, 5.72; N, 5.84; Cl, 14.45.

Compound **18a** eluted subsequently, yield 1.2 g (20%) (amorphous yellow solid); ^1H nmr (deuteriochloroform): δ 0.87 (m, 2H), 2.36 (m, 1H), 3.17 (t, 1H), 3.43 (m, 1H), 3.62 (m, 1H), 3.90 (dd, 1H), 4.44 (d, 1H), 4.70 (dd, 1H), 4.98 (d, 1H), 5.25 (s, 1H), 6.12 (m, 3H), 6.22 (s, 1H), 6.63 (s, 1H), 6.91 (s, 1H), 7.19-7.61 (m, 10H).

Anal. Calcd. for $C_{30}H_{27}ClN_2$: C, 79.9; H, 6.03; N, 6.21; Cl, 7.86. Found: C, 80.02; H, 6.23; N, 6.11; Cl, 7.84.

6-Iodomethyl-7-phenyl-5,6-dihydroindolizine **17b**.

By the same procedure as described for the preparation of **17a** starting from **16a** but using hydriodic acid in tetrahydrofuran in place of hydrochloric acid **17a** was obtained in 37% yield mp, 67-69°; ^1H nmr (deuteriochloroform): δ 3.06 (dd, 1H), 3.34 (m, 2H), 4.02 (dq, 1H), 4.48 (dd, 1H), 6.23 (t, 2H), 6.74 (t, 1H), 6.94 (s, 1H), 7.25-7.54 (m, 5H).

Anal. Calcd. for $C_{15}H_{14}IN$: C, 53.75; H, 4.21; N, 4.18. Found: C, 53.98; H, 4.23; N, 4.25.

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