Studies on Pyrrolidinones. Derivatives of 1,2,3,5,10,10a-Hexahydrobenz[*f*]indolizine-3,10-dione

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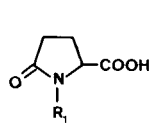
The Friedel-Crafts reaction of *N*-(arylmethyl)-5-pyrrolidinone-2-carboxylic acids gives either a cyclization or a reaction with benzene (used as a solvent). Reactions such as reduction, keto substitution and lactam ring opening of 1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3,10-diones obtained by the method above have been studied.

J. Heterocyclic Chem., **20**, 893 (1983).

Within the scope of a general research on cyclized derivatives of 5-pyrrolidinone-2-carboxylic acid (pyroglutamic acid) (**1**) [1] we have studied the cyclization of the *N*-(arylmethyl)-5-pyrrolidinone-2-carboxylic acids into new derivatives, 1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3,10-diones (**13**) [7] and some reactions of those ketones.

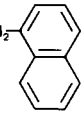


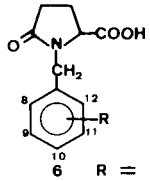
1 R_1 = H

2 R_1 = CH_2Ar

3 R_1 = 

4 R_1 = 

5 R_1 = 



6 R = H

7 R = $_{10}CH_3$

8 R = $_{8}CH_3$

9 R = $_{10}Cl$

10 R = $_{8}Cl$

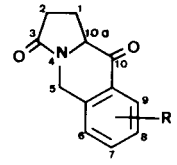
11 R = $_{10}Br$

12 R = $_{9}CF_3$

FIGURE I

Cyclization of *N*-(Arylmethyl)pyroglutamic Acids (**2**).

First tests were performed with *N*-benzylpyroglutamic acid (**6**). The expected ketone was not obtained from the reaction with polyphosphoric acid [2] [3] or sulfuric acid [4]. The best method is the Friedel-Crafts intramolecular cyclization which was studied with a systematic variation of solvent, temperature, duration of reaction and ratio of catalyst to *N*-benzylpyroglutamic acid chloride. The choice of a solvent was found important for the yields of the reaction: nitrobenzene, methylene dichloride, 1,2-dichloro ethane or heptane [4] [5] used with aluminium trichloride or tin tetrachloride at ambient temperature or with reflux gave poor results. 1,2,3,5,10,10a-Hexahydrobenz[*f*]indolizine-3,10-diones (**13**) were obtained in satisfactory yields using benzene as a solvent and aluminium trichloride as a catalyst; the ketone **21** formed by Campaigne and Matthews [6] in the reaction of the acid **6** with phenyl magnesium bromide could not be detected. Benzene and aluminium trichloride were then used for the cyclization of acids **5**, **7** and **8** and gave ketones **14**, **15** and **19** in good yields. The presence of a halogen on the aromatic ring (acids **9**, **10** and **11**) decreased the yields of the cyclized product with parallel formation of solvent acylation products **22**, **23** and **24**. When the benzene ring was substituted with a CF_3 group (**12**), and with *N*-(2-thenyl)pyroglutamic acid (**3**), the cyclization could not be realized. The ketone **20** could only be obtained in poor yields, when the acid chloride of **4** was used with tin tetrachloride as a catalyst.



13 R = H

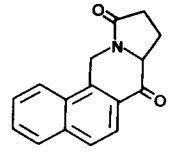
14 R = $_{8}CH_3$

15 R = $_{8}CH_3$

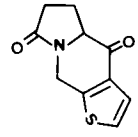
16 R = $_{8}Cl$

17 R = $_{8}Cl$

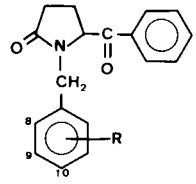
18 R = $_{8}Br$



19



20



21 R = H

22 R = $_{10}Cl$

23 R = $_{8}Cl$

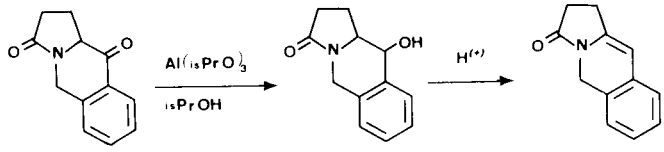
24 R = $_{10}Br$

FIGURE II

Reduction of 1,2,3,5,10,10a-Hexahydrobenz[*f*]indolizine-3,10-diones (**13**).

The ketone or the lactam group of heterocycle **13** can be selectively reduced: The Merwein-Verley-Pondorf reaction applied to the ketone **13** gave the alcohol **25** obtained as a single isomer which can be dehydrated as an ethylene derivative **26**. The product is fairly unstable and quickly decomposes at ambient temperature.

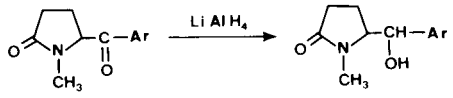
SCHEME 1



13 25 26

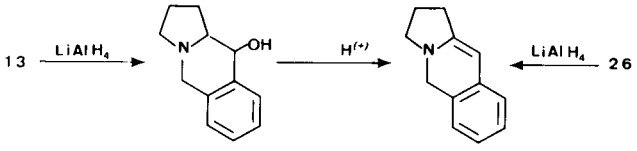
Kolocouris used lithium aluminium hydride to reduce the keto group in the presence of a lactam group [8] (Scheme 2). In the present case, both carbonyl groups were reduced using an excess of the reagent (Scheme 3).

SCHEME 2



The reduction of the lactam **26** or the dehydration of the amino alcohol **27** gave a liquid (assumed to be the enamine **28**) which decomposes within a few minutes and therefore cannot be identified.

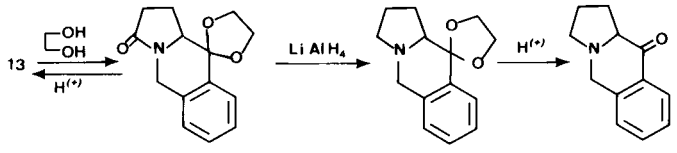
SCHEME 3



27 28

The selective reduction of the lactam group was obtained when the keto group was protected as a dioxolane. The product **30** thus formed proved to be less sensitive to acidic hydrolysis than dioxolane **29** but nevertheless yielded quantitatively the amino ketone **31**.

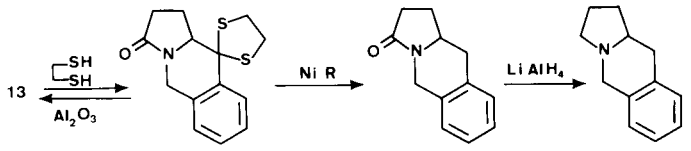
SCHEME 4



29 30 31

The selective reduction of the keto group was obtained when dithiolane **32** was reacted with Raney nickel (**9**). Lactam **33** was obtained and subsequently converted into the amine **34** which was already known [7].

SCHEME 5

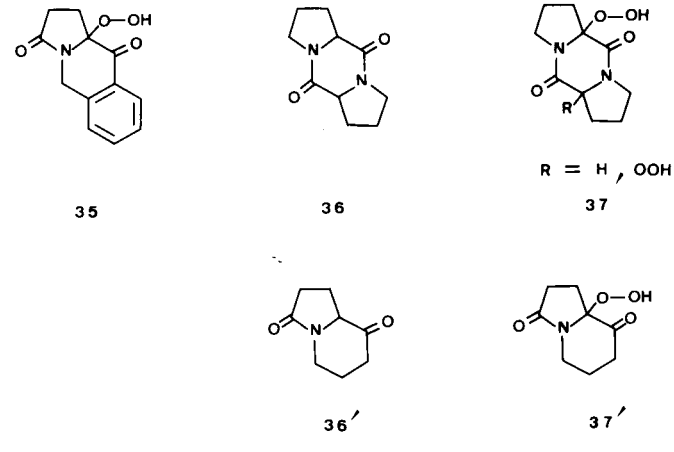


32 33 34

Substitution of 1,2,3,5,10,10a-Hexahydrobenz[*f*]indolizine-3,10-dione in the 10a Position.

Indolizine **13** proved to be a fairly unstable white solid product. The pure product became yellow within a few days and its melting point significantly decreased within a few weeks. This degradation slowed down at 0° and was almost negligable at −60° or, in the absence of air, at ambient temperature. We assumed a radical reaction of oxygen with the 10a hydrogen giving a hydroperoxide **35**. It is worth pointing out that the products **36** and **36′** which have a fairly similar chain structure gave hydroperoxides **37** and **37′** upon reaction with oxygen [10].

SCHEME 6

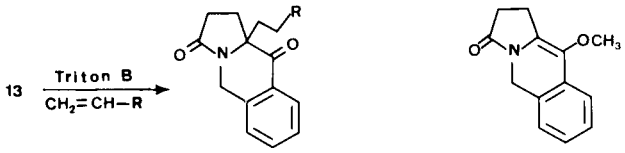


35 36 37

36′ 37′

Attempted methylation of ketone **13** by Conia's method [11] gave a mixture of products, one of which could be isolated and identified with the enol ether **44**. Introduction of various chains in position 1a (products **38, 39** and **40**) was realized using the Michael reaction. However, this last method failed when steric hindrance became too important (with mesityl oxide for instance). These compounds (**38, 39** and **40**) are stable; this fact justifies the above assumption as to the possible reasons for the degradation of compound **13**.

SCHEME 7



38 R = C≡N

39 R = C(=O)-CH3

40 R = C(=O)-O-C2H5

Table I

Yields and Physical Data of Indolizinediones **13-20**

Compound No.	Yield %	Mp °C Bp °C (mm Hg)	IR: ν cm^{-1} (nujol)	NMR: δ ppm (deuteriochloroform)
13	73	107-108 —	1690, 1600, 760	2.44 (s), 2.48 (s) (4H), 4.17-4.45 - 5.09-5.38 (2H) (J = 16.8 Hz), 4.32 (1H) (t), 7.17-7.8 (m), 7.95-8.12 (d) (4H)
14	71	129-130 —	1690, 1600, 780	2.28 (3H), 2.35 (s), 2.42 (s) (4H), 3.90-4.20 - 4.93-5.23 (2H) (J = 18 Hz), 4.20 (1H) (t), 7.05-7.5 (m) (2H), 7.72-7.85 (d) (1H)
15	64	92-93 173 (0.05)	1690, 1600, 880, 830	2.48 (s), 2.56 (s) (4H), 4.32-4.62 - 5.30-5.60 (2H) (J = 18 Hz), 4.40 (1H) (t), 7.45-7.58 - 7.70-7.83 (2H) (J = 8.1 Hz), 8.22 (1H)
16	18	125-126 —	1690, 1600 870, 830	2.43 (s), 2.48 (s) (4H), 4.14-4.43 - 5.08-5.37 (2H) (J = 17.4 Hz), 4.32 (1H) (m), 7.19-7.32 - 7.47-7.60 (J = 7.8 Hz), 7.97 (d) (3H)
17	5	126-127 195 (0.2)	1690, 1600, 760, 705	2.40 (s), 2.45 (s) (4H), 3.92-4.22 - 5.07-5.37 (2H) (J = 18 Hz), 4.22 (1H) (m), 7.04-7.50 (m), 7.68-7.82 (d) (3H)
18	30	147-148 —	1690, 1600, 830	2.40 (s), 2.45 (s) (4H), 4.08-4.37 - 5.02-5.31 (2H), (J = 17.4 Hz), 4.25 (1H) (m), 7.11-7.26 - 7.55-7.70 (J = 9 Hz), 8.08 (d) (3H)
19	84	135 —	1690, 1610, 800, 740	2.38 (s), 2.44 (s) (4H), 4.22-4.52 - 5.44-5.74 (2H) (J = 18 Hz), 4.22 (1H) (m), 7.20-8.10 (6H) (m)
20	13	136 —	1680, 1530, 870, 850, 820, 800, 760, 740	2.45 (s), 2.50 (s) (4H), 4.21-4.50 - 5.32-5.61 (2H) (J = 17.5 Hz), 4.3 (1H) (m), 7.17-7.26 - 7.37-7.46 (J = 5.5 Hz) (2H)

Table II

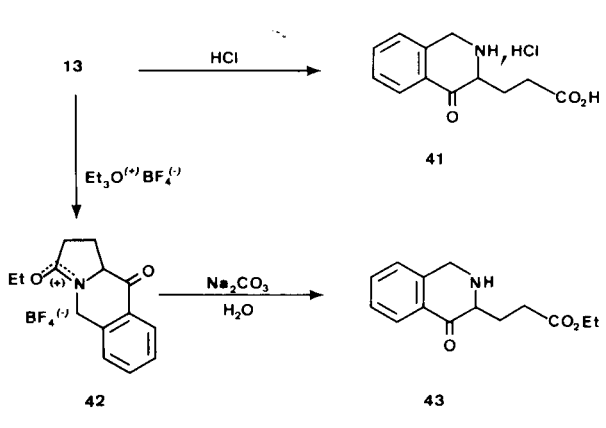
Yields and Physical Data of 1-Benzyl-5-benzoyl-2-pyrrolidinones

Compound No.	Yield %	Bp °C (mm Hg)	IR: ν cm^{-1} (neat)	NMR: δ ppm (deuteriochloroform)
22	25	215 (0.1)	1690, 1615, 1600, 820, 770, 710	1.7-2.8 (4H), 3.7-3.95 - 5.03-5.28 (2H) (J = 15 Hz), 4.88 (1H) (t), 7-8.2 (9H) (m)
23	31	218 (0.1)	1700, 1610, 1600, 770, 730, 710	1.7-2.7 (4H), 4.01-4.26 - 5.03-5.28 (2H) (J = 15 Hz), 5.02 (1H) (t), 7-7.95 (9H) (m)
24	31	230 (0.1)		1.7-2.9 (4H), 3.71-3.96 - 5.11-5.36 (2H) (J = 15 Hz), 4.90 (1H) (m), 7.03-8.10 (9H) (m)

Lactam Ring Opening. 1,2,3,4-Tetrahydro-4-isoquinolones.

The acid hydrolysis of indolizine **13** gave the amino acid hydrochloride **41** in an impure state and with poor yields. The basic hydrolysis [12] of the imino ether fluoroborate **42** gave 3-(2-carbethoxyethyl)-1,2,3,4-tetrahydroisoquinol-4-one **43** as a pure compound. To our knowledge, little has been reported on these types of compounds.

SCHEME 8



EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded on a "Perkin Elmer 700" spectrometer, and the nmr spectra on a "Jeol 60" at 60 MHz, using tetramethylsilane as an internal reference. Elemental analyses were performed by the "Central Microanalytical Department"

Table III

Yields and Physical Data of the Derivatives of the Ketone **13**

Compound No.	Yield %	Mp °C Bp °C (mm Hg)	IR: ν cm^{-1} (nujol)	NMR: δ ppm (deuteriochloroform)
25	65	146 —	3340, 1660, 1060	1.8-2.7 (4H) (m), 3.3-3.7 (1H) (m), 3.99-4.28 - 4.71-4.90 (2H) (J = 17.5 Hz), 4.04 (1H) (s; mix with deuterium oxide), 4.28-4.43 (1H) (J = 9 Hz), 6.9-7.8 (4H) (m)
26	67	128 150 (0.3)	1718, 1660	2.3-3.1 (4H) (sym mult), 4.77 (2H) (s), 6.7-7.4 (5H) (m)
27	80	135-136 —	3150, 1060	1.25-2.4 (6H) (m), 3,09 (2H) (s, 1H mix with deuterium oxide), 3.09-3.33 - 3.72-3.96 (2H) (J = 14.4 Hz), 4.26-4.38 (1H) (J = 7.2 Hz), 6.75-7.55 (4H) (m)
29	83	104 —	1690	1.90-2.70 (4H) (m), 3.80-4.60 (5H) (m), 4.10-4.39 - 4.89-5.28 (2H) (J = 17.4 Hz), 7.05-7.60 (4H) (m)
30	79	— 115 (0.05)	1700, 1610, 765 (neat)	1.7-2.0 (4H) (m), 2.1-2.8 (2H) (m), 3.1-3.45 (1H) (m), 3.27-3.52 - 4.03-4.28 (2H) (J = 15 Hz), 3.95-4.5 (4H) (m), 6.9-7.6 (4H) (m)
31·HCl	100	173 —	1700, 1610, 760 (neat)	Solvent: deuterium oxide 2-2.9 (4H) (m), 3.75 (2H) (t), 7.5-8.3 (4H) (m)
33·HCl	69	60-61 —	1680, 1590, 1500, 765 (neat)	1.9-2.7 (m) (4H), 2.82-2.90 (2H) (d), 3.3-3.95 (1H) (m), 4.05-4.34 - 4.76-5.05 (2H) (J = 17.5 Hz), 7.11 (4H) (s)
34·HCl	83	120-123 (27-28 free base)		Solvent: deuterium oxide 1.20-2.50 (6H) (m), 2.6-2.95 (2H) (m), 3-3.4 (1H) (m), 3.21-3.45 - 3.96-4.20 (2H) (J = 14.4 Hz), 7.07 (4H) (s)
38	57	— 255 (0.2)	2270, 1700, 1610, 1490, 760 (neat)	1.80-2.80 (8H) (m), 4.10-4.40 - 5.10-5.40 (2H) (J = 18 Hz), 7.15-8.15 (4H) (m)
39	83	92-94 —	1700, 1610, 760	1.85-2.80 (8H) (m), 2.10 (3H) (s), 4.13-4.43 - 5.12-5.42 (2H) (J = 18 Hz), 7.20-8.20 (4H) (m)
40	86	118 —	1710, 1610, 780	1.22 (3H) (t) (J = 7 Hz), 1.85-2.8 (8H) (m), 2.08 (2H) (q) (J = 7 Hz), 4.15-4.45 - 5.12-5.42 (2H), (J = 18 Hz), 7.2-7.8 (3H) (m), 7.9-8.2 (1H) (m)
43·HCl	36	164 —	1730, 1710, 1580, 1600, 765	Solvent: deuterium oxide 1.20 (3H) (t) (J = 7.2 Hz), 2.05-2.90 (5H) (m), 4.10 (2H) (q) (J = 7.2 Hz), 4.2-4.4 (2H) (m), 7.3-8.15 (4H) (m)
44	ϵ	— 162 (0.25)	1710, 1660, 760	2.35-3.10 (4H) (sym mult), 3.72 (3H) (s), 4.22 (2H) (s), 6.90-7.40 (4H) (m)

of CNRS in Thiais, France and are listed in Table IV. All yields and physical properties of the products are given in Tables I, II and III.

N-Benzylpyroglutamic Acid Chloride.

A mixture of acid **6** (8.6 g, 0.372 mole), 80 ml of thionyl chloride and 3 drops of pyridine was heated at 65-70° in a water bath during 20 minutes. The pale yellow solution was evaporated using a rotoevaporator and subsequently under vacuum.

This method was used for all *N*-arylmethylpyroglutamic acid chlorides.

1,2,3,5,10,10a-Hexahydrobenz[*f*]indolizine-3,10-dione (**13**).

The above chloride was dissolved in 160 ml of benzene and added within 30 minutes to a suspension of 163.2 g (1.223 moles) of aluminium trichloride in 400 ml of benzene. The suspension was mixed with a mechanical stirrer and heated at 55° until no more gas was evolved (roughly 30 minutes), and then 5 minutes to 65°. The mixture was then cooled and hydrolyzed with a minimum amount of water and ice. The aqueous phase was extracted with methylene chloride. The organic phases were washed with water, dilute sodium hydroxide and water. After drying with sodium sulfate the solvents were evaporated. The precipitate was washed with ether and recrystallized twice from acetone. The same method was used to obtain the ketones **14**, **15** and **19**.

6-Chloro-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3,10-dione (**17**) and 1-(*o*-Chlorobenzyl)-5-benzoylpyrrolidin-2-one (**23**).

To a suspension of the chloride obtained from 30 g (0.118 mole) of acid **10** in 150 ml of benzene, at ambient temperature, 14.9 g (0.118 mole) of aluminium trichloride was added as a catalyst. A vigorous reaction was observed. This procedure was repeated twice, each time when the reaction of the preceding one was over. The mixture was refluxed during 30 minutes and then stirred during 2.5 hours at ambient temperature. After hydrolysis, extraction and evaporation, the residue was fractionated under vacuum. The ketones **17** and **23** were obtained. The former was recrystallized from acetone; the latter was a viscous liquid.

The same method as described above for **17** and **23** was used to obtain ketones **16** and **22** as well as **18** and **24**.

1,2,3,5,9,9a-Hexahydrothieno[2,3-*f*]indolizine-3,9-dione (**20**).

To a cooled solution (0°) of the acid chloride obtained from 10 g (0.04 mole) of acid **4** and 90 ml of benzene, 11 g (0.042 mole) of tin tetrachloride was added within 10 minutes. The mixture was allowed to stand for one hour at 0-5° and then heated during 10 minutes at 45°. After cooling, hydrolyzing and extracting with methylene chloride, the product was washed with water, diltute sodium hydroxide, and water. Many resins were extracted upon washing with sodium hydroxide. After drying and evaporating the solvents, compound **20** was treated twice in acetone with activated carbon.

10-Hydroxy-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizin-10-one (**25**).

The ketone **13**, 3.9 g (0.019 mole), was added to 6 g (0.03 mole) of

Table IV

Microanalyses of New Compounds

Compound No.	Calcd. C	H	N	O	Found C	H	N	O
13	71.62	5.51	6.96		71.52	5.51	7.02	
14	72.56	6.05	6.51		72.47	6.03	6.64	
15	72.56	6.05	6.51		72.31	5.86	6.41	
16	61.15	4.25	5.95	13.59	60.85	4.49	5.96	13.68
17	61.15		5.95	13.59	61.41		5.98	13.80
18	51.43	3.57	5.00	11.43	51.49	3.60	4.70	11.60
19	76.49	5.18	5.38	12.75	76.68	5.32	5.70	12.87
20	57.97	4.35	6.76	15.46	58.10	4.35	6.77	15.19
22	68.90	5.10	4.47	10.20	68.76	5.18	4.48	10.47
23	68.90	5.10	4.47	10.20	68.79	4.98	4.64	10.50
24	60.34	4.47	3.91	8.94	60.09	4.55	4.05	8.99
25	70.93	6.40		15.76	71.25	6.53		15.88
26	77.84	5.94	7.57	8.65	77.52	5.95	7.62	8.71
27	76.18	7.83	7.40	8.46	75.95	8.14	7.62	8.70
29	68.61	6.12	5.71	19.56	68.14	6.28	5.97	19.57
30	72.72	7.36		13.85	72.80	7.56		13.95
31·HCl	64.43	6.26	6.27	7.16	64.15	6.26	6.17	7.29
33	77.00	6.95	7.49	8.56	77.01	6.99	7.68	8.35
34	83.24	8.67	8.09		82.94	8.55	8.30	
38	70.87	5.51	11.02	12.59	71.03	5.76	11.05	12.41
39	70.85	6.27	5.17	17.71	70.90	6.41	5.07	18.06
40	67.76	6.35	4.65	21.34	67.63	6.39	4.70	21.14
43·HCl	59.47	6.02	4.95	16.99	59.42	6.31	5.12	16.99

aluminium isopropylate and refluxed in 30 ml of anhydrous isopropyl alcohol; acetone given off was simultaneously removed. The reaction was stopped when a 2,4-dinitrophenylhydrazine test was negative. The isopropyl alcohol was evaporated and the mixture was acidified with cold dilute hydrochloric acid and extracted with chloroform. After washing with dilute sodium bicarbonate then water, the solution was dried and the chloroform was evaporated. The product was crystallized in ether and was then recrystallized from acetone.

1,2,3,5-Tetrahydrobenz[*f*]indolizin-3-one (**26**).

A mixture of 2.6 g (0.0128 mole) of alcohol **25** and 1.8 g of potassium hydrogen sulfate was heated under vaccuum in an oil bath at 180°. The ethylene compound was distilled off as it was formed, and immediately crystallized into fine yellow powder which was first recrystallized from benzene and then from acetone.

10-Hydroxy-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine (**27**).

The ketone **13**, 5 g (0.025 mole) in 150 ml of tetrahydrofuran was added within 10 minutes to 2 g (0.054 mole) of lithium aluminium hydride in 100 ml of tetrahydrofuran. The mixture was refluxed during 16 hours and then cooled. The hydride excess was destroyed with ethyl acetate and hydrolysis was carried out with 50 ml of water. After extracting with chloroform, the mixture was dried and the solvent was evaporated. The product was recrystallized from acetone.

10-Ethylenedioxy-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizin-3-one (**29**).

A solution made up with 5 g (0.025 mole) of ketone **13**, 64 ml (1.13 mole) of ethylene glycol and 0.3 g of monohydrated *p*-toluenesulfonic acid was placed in a round bottomed flask fitted with a Soxhlet extractor filled with sodium sulfate. The mixture was refluxed during 40 hours and neutralized with a solution of sodium carbonate, extracted twice with 100 ml of chloroform, washed with water, dried, and the solvent was evaporated. The precipitate obtained was recrystallized from acetone. Dioxolane **29** (0.5 g) was heated at 70° during 15 minutes with 115 ml of water and 1 ml of concentrated hydrochloric acid. Extraction was carried out with chloroform and the product was washed with sodium hydrogenocarbonate solution and dried. The solvent was evaporated and the compound was precipitated by ether. The yield was 90% of ketone **13**.

10-Ethylenedioxy-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine (**30**).

The amide **29** was reduced following the same procedure described for **27**. After evaporation of the solvents, a small amount of impurities could be filtered out, ether was added to the filtrate and 5 ml of concentrated hydrochloric acid was added which gave the aminodioxolane hydrochloride **30**. The precipitated product was dissolved in water and was neutralized with dilute sodium hydroxide, extracted with ether and distilled. Dioxolane **30** was obtained as a slightly coloured liquid.

1,2,3,5,10,10a-Hexahydrobenz[*f*]indolizin-10-one (**31**).

The aminodioxolane **30** (7.8 g) in 50 ml of concentrated hydrochloric acid and 30 ml of water was heated at 50° during 15 minutes. After cooling, 100 ml of ether was added and the mixture was neutralized with a dilute solution of potassium hydroxide. Extraction was carried out with dichloromethane. After drying and evaporation of the solvents, the aminoketone **31** was obtained as a slightly coloured liquid. The hydrochloride derivative is quantitatively obtained by adding concentrated hydrochloric acid to a methanol solution of **31**.

1,2,3,5,10,10a-Hexahydrobenz[*f*]indolizin-3-one (**33**).

To a mixture of 10 g (0.05 mole) of ketone **13** and 10 ml of ethane-1,2-dithiol, 10 ml of boron trifluoride etherate solution was added. After mixing for 10 minutes, 30 ml of methanol was added and the mixture was allowed to stand during 48 hours at −60°; 10.7 g of dithiolane **32** was obtained. Dithiolane **32**, 4 g (0.014 mole) was dissolved in 150 ml of absolute ethanol and added into 50 ml of Raney nickel W-2 suspension in ethanol prepared according to [13]. The mixture was refluxed during 2 hours, filtered and the solvents were evaporated under vacuum. The product obtained crystallized after several days at 0° and was recrystallized from ether.

1,2,3,5,10,10a-Hexahydrobenz[*f*]indolizine (**34**).

The lactam **33**, 1.5 g (0.08 mole) was added in 3 steps to a suspension of 0.4 g (0.01 mole) of lithium aluminium hydride in 60 ml of anhydrous ether. After refluxing during 24 hours, the excess of hydride was destroyed with ethyl acetate and hydrolysis was carried out with water. The solvents were filtered, dried and evaporated. The amine hydrochloride of **34** was obtained by reacting an ether solution of the amine with dry hydrogen chloride. It was recrystallized from a mixture of methanol and ether. The amine was obtained after reaction with an excess of ammonia solution and was extracted with ether. After evaporating the solvent, the indolizine **34** was obtained as a liquid which crystallized after several days at 0°.

10a-Cyanoethyl-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3,10-dione (**38**).

A benzyltrimethyl ammonium hydroxide solution (Triton B) (0.5 ml, 40% in methanol) was very slowly added with a good stirring to 5 g (0.024 mole) of the ketone **13** in 50 ml of acrylonitrile. After standing for 2 hours at ambient temperature, the excess reagent was evaporated and the nitrile **38** was distilled under vacuum. The product was a liquid which was stable when exposed to air.

10a-(3-Oxobutyl)-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3,10-dione (**39**).

Methyl vinyl ketone (1.9 g, 0.0271 mole) was added very slowly at ambient temperature with good stirring to 5 g (0.0248 mole) of ketone **13** in 50 ml of anhydrous methanol, followed by 0.5 ml of Triton B solution. The mixture was then refluxed for one hour. After evaporating the solvent, the product was dissoived in dichloromethane, washed with water, dried and filtered on neutral activated alumina. The product obtained after evaporation crystallized after a few days; the crystals were washed with ether.

The same method was used to obtain the ester **40**.

3-(2-Carbethoxyethyl)-1,2,3,4-tetrahydroisoquinolin-4-one (**43**).

To 5 g (0.0248 mole) of the ketone **13** in 100 ml of dichloromethane was slowly added an equimolar amount of triethyl oxonium fluoroborate [14]. The solution was mixed for 30 minutes. Hydrolysis was carried out with an excess solution of sodium carbonate, and the aqueous phase was extracted with dichloromethane. The organic phases were washed with water, dried and evaporated, yielding 5.6 g of a liquid. A precipitate of **43** was formed after dissolving in 30 ml of absolute ethanol and acidifying with an ethanol solution of hydrochloric acid. The precipitate **43** was filtered and washed with absolute ethanol; 56% of the initial amount of ketone **13** can be recovered through neutralization of the ethanol solution with sodium hydrogen carbonate.

10-Methoxy-1,2,3,5-tetrahydrobenz[*f*]indolizin-3-one (**44**).

Anhydrous *t*-amyl alcohol, 10.2 g (0.14 mole) was heated at 80° with 450 ml of benzene and 2.3 g (0.058 g-atom) of potassium. After the potassium had disappeared, 10 g (0.049 mole) of the ketone **13** was added and the mixture was refluxed for one hour. Methyl bromide (20 ml) was then added and reflux was carried out for one hour. The solution was washed with water, dried, evaporated and the product distilled. The fraction $E_{0.02}$ = 162-165° was treated with a mixture of 1/1 benzene/cyclohexane and yielded enough ether enol **44** in order to analyze the sample by ir and nmr (insufficient for elemental analysis) (see Table III).

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