Potential Antitumor Agents. III. Synthesis of Pyrazolo[3,4-*e*]pyrrolo[3,4-*g*]indolizine and 1*H*-Pyrazolo[3,4-*e*]indolizine Derivatives

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The preparation of 5-dimethylaminoethyl-4,6-dioxo-1-phenyl-1,4,5,6-tetrahydropyrazolo[3,4-*e*]pyrrolo-[3,4-*g*]indolizine, a derivative of the still unknown tetracyclic parent ring pyrazolo[3,4-*e*]pyrrolo[3,4-*g*]indolizine, is reported starting from 1-phenyl-5-(1-pyrryl)pyrazole-4-acetonitrile by PPA catalyzed double cyclization of the related oxalylcyanomethyl derivative and subsequent alkylation. The synthesis of 4,5-bis(isopropylaminocarbonyloxymethyl) and 4,5-bis-(cyclohexylaminocarbonyloxymethyl) derivatives of 1-phenyl-1*H*-pyrazolo[3,4-*e*]indolizine is also described. The new tricyclic and tetracyclic derivatives were tested as potential antitumor agents.

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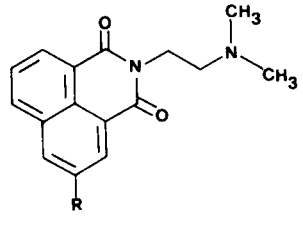
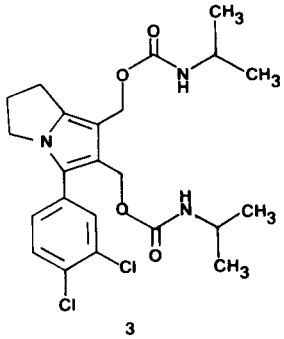
N-(Aminoalkyl)imide antineoplastic agents and antileukemic biscarbamates have been deeply investigated in the last few years [1-7]. Researches of Cheng [1] indicate that a [2-(substitutedamino)ethyl]amino chain attached to proper polycyclic ring systems is crucial for displaying antineoplastic activities. Analogous biological activities were found to be produced when an *ortho* bis-(isopropylaminocarbonyloxymethyl) alkylating system was present in the pyrrole, dihydropyrrolizine, pyrrolo[2,1-*a*]isoquinoline or other related heterocycles. Bis-(carbamoyloxymethyl) derivatives belong to the so-called "acylated vinilogous carbinolamines" class of antineoplastic agents [2-7].

Cheng and Anderson systematic studies led to the discovery of Mitonafide **1**[1], NSC-308847 **2** [8] and the dihydropyrrolizine biscarbamate NSC-278214 **3** [8], respectively. These compounds have been shown to possess significant activities against a wide range of experimental and human tumors and are chemical structures of interest to the Division of Cancer Treatment of the National Cancer Institute (Bethesda, Maryland).



1 R = NO_2
2 R = NH_2



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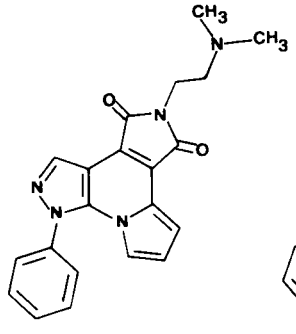
Our interest in new tricyclic ring systems [9-13] resembling the pyrrolo[3,2-*e*]indole subunits (*e.g.* the antileukemic portion PDE I) of the powerful antitumor antibiotic CC-1065 [14] led us to synthesize 1*H*-pyrazolo[3,4-*e*]indolizine derivatives structurally related to compounds **1-3**. The present work, therefore, deals with the synthesis of derivatives **4-6**.



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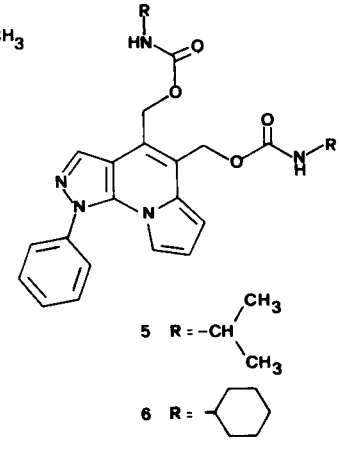
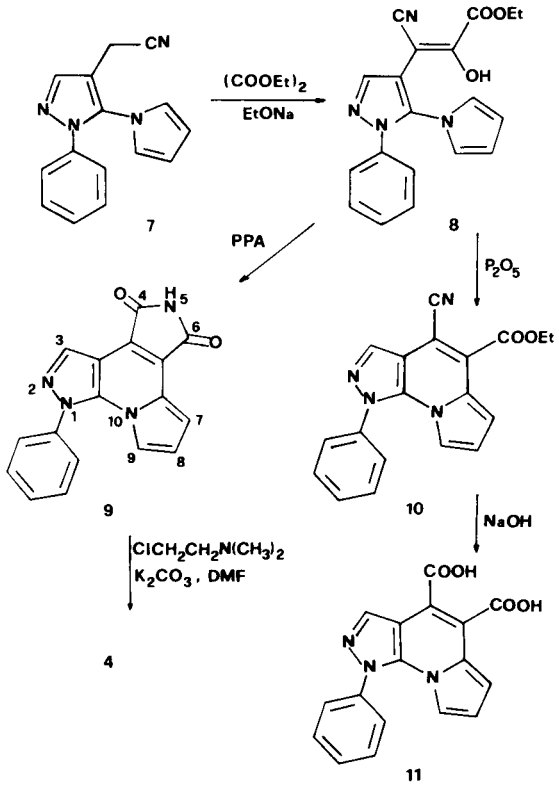


5 R = -CH(CH3)2
6 R = cyclohexyl

Claisen reaction between diethyl oxalate and 1-phenyl-5-(1-pyrryl)pyrazole-4-acetonitrile **7** [9] in the presence of sodium ethoxide afforded the oxalyl derivative **8** (Scheme 1). This compound could be a key intermediate for the preparation of both tetracyclic and tricyclic derivatives represented by formulas **4-6**. In fact, treatment of **8** with polyphosphoric acid (PPA) afforded in good yield the imide **9**, probably by cyclodehydration followed by sequential hydrolytic-cyclizing steps, whereas the use of phosphorus

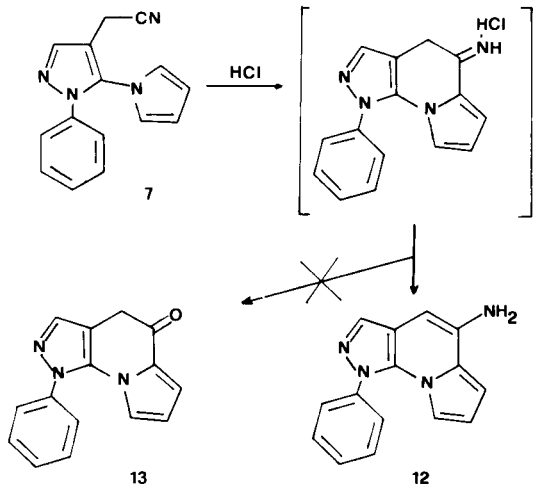
pentoxide as dehydrating agent furnished the expected cyanoester **10**. Compound **9**, a derivative of the still unknown tetracyclic ring pyrazolo[3,4-*e*]pyrrolo[3,4-*g*]indolizine, has been transformed into **4** by alkylation with 2-dimethylamino-1-chloroethane in DMF in the presence of dry potassium carbonate. Alkaline hydrolysis of **10** with 10% sodium hydroxide gave the corresponding dicarboxylic acid **11**, but any attempt to transform this compound into the diol **18** by standard procedures failed.

Scheme 1



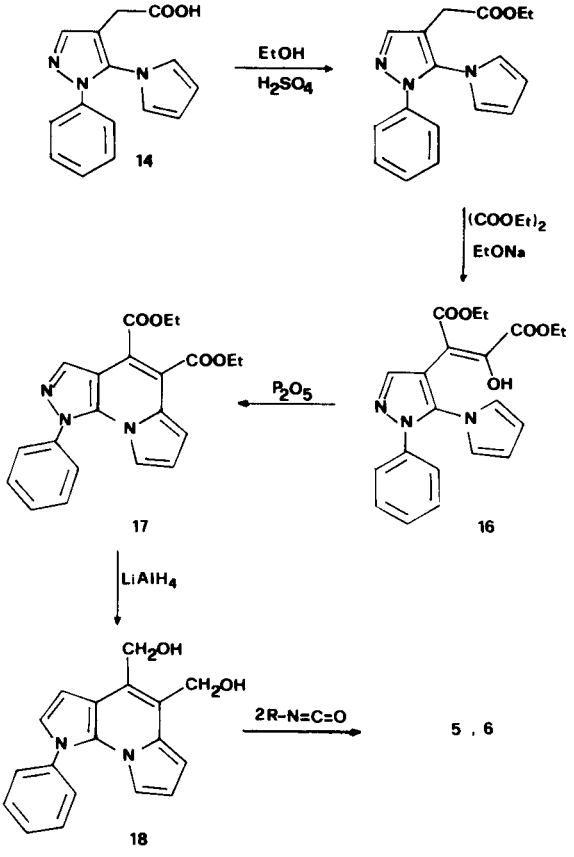
Compound **18**, required for the synthesis of biscarbamates **5** and **6**, was obtained by a pathway having as starting material 1-phenyl-5-(1-pyrryl)pyrazole-4-acetic acid **14** previously prepared [11] from the nitrile **7**. Hydrolysis of the latter derivative led to different products depending on the hydrolyzing agent employed. In alkaline medium (10% sodium hydroxide) the required acid **14** was promptly obtained [11], whereas the use of concentrated hydrochloric acid according to the Hoesch cyclization, gave 5-amino-1-phenyl-1*H*-pyrazolo[3,4-*e*]indolizine **12** as the only product. The formation of **12** instead of the expected ketone **13** is due to the fact that the ketimine formed on cyclization of the **7** imino-hydrochloride intermediate is unaffected by the hydrolytic medium being stable in the tautomeric amine form (Scheme 2).

Scheme 2



Esterification of **14** with dry ethanol in the presence of concentrated sulfuric acid afforded the corresponding ethyl ester **15**. This compound was subjected to Claisen condensation with ethyl oxalate and sodium ethoxide to

Scheme 3



give the oxalyl diester **16**. Cyclodehydration of **16** with phosphorus pentoxide led to the dicarboxylic diester **17**, which was then reduced by lithium aluminum hydride to the required diol **18**. On reaction with the proper isocyanate, **18** furnished the biscarbamates **5** and **6** (Scheme 3).

Derivatives **4-6**, **9-11**, **17**, **18**, 1-phenyl-1*H*-pyrazolo-[3,4-*e*]indolizine and its 4-cyano derivative [9] have been tested for antitumor activity against P388 lymphocytic leukemia in mice under developmental therapeutics program of National Cancer Institute (Bethesda, Maryland) according to the protocol [15] adopted by the Division of Cancer Treatment. Table 1 includes data of screening. A compound is considered active when the ratio T/C (survival times for treated to control tumor-bearing mice) is higher than 120; test is toxic when T/C is lower than 85.

Table 1

Activity Against P388 Mouse Leukemia

Compound	NCI No.	Dose (mg/kg)	T/C (%)
4	614523	240.0	100
		120.0	102
		60.0	100
5	614519	240.0	96
		120.0	91
		60.0	89
		30.0	97
6	614522	240.0	99
		120.0	92
		60.0	Tox
		30.0	89
		15.0	93
9	614520	240.0	Tox
		120.0	Tox
		60.0	Tox
		30.0	87
		15.0	96
		7.5	96
10	614516	240.0	Tox
		120.0	Tox
		60.0	91
		30.0	96
		15.0	98
11	614517	240.0	100
		120.0	100
		60.0	102
17	614521	240.0	91
		120.0	93
		60.0	99
18	614518	240.0	89
		120.0	90
		60.0	100
19 [a]	614524	240.0	89
		120.0	98
		60.0	105
20 [b]	614525	240.0	120
		120.0	111
		60.0	108

[a] 4-Cyano-1-phenyl-1*H*-pyrazolo[3,4-*e*]indolizine [9]. [b] 1-Phenyl-1*H*-pyrazolo[3,4-*e*]indolizine [9].

All tested compounds resulted toxic or inactive (T/C included between 86 and 120). The 4,5-unsubstituted 1-phenyl-1*H*-pyrazolo[3,4-*e*]indolizine showed the highest ratio (T/C = 120) at 240 mg/kg dose. Screening was performed by Institut Jules Bordet, Brussels (Belgium).

EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra (nujol mulls) were run on a Perkin-Elmer 297 spectrophotometer. The pmr spectra were recorded on a Varian EM-390 spectrometer with TMS as the internal standard. Merck silica gel and alumina (70-230 mesh ASTM) were used for chromatographic purifications. Microanalyses were performed by A. Pietrogrande, Padova, Italy.

α-Ethoxyoxalyl-1-phenyl-5-(1-pyrryl)pyrazol-4-acetonitrile (**8**).

To a solution of sodium ethoxide, prepared by dissolving sodium (2.42 g, 0.105 g-atom) in absolute ethanol (35 ml), diethyl oxalate (16.1 g, 0.11 mole) and finely powdered 1-phenyl-5-(1-pyrryl)pyrazole-4-acetonitrile **7** [9] (26.3 g, 0.105 mole) were sequentially added. After stirring for 20 hours at room temperature, the reaction was quenched with water, brought to *p*H 2 by adding 1*N* hydrochloric acid and extracted with ethyl acetate. The combined organic solution was washed with brine and dried over anhydrous sodium sulfate. Removal of the solvent afforded 22.3 g (61%) of oily α-ethoxyoxalyl-1-phenyl-5-(1-pyrryl)pyrazole-4-acetonitrile **8**, homogeneous by tlc (silica gel-ethyl acetate), which was used in the next step without further characterization.

4,6-Dioxo-1-phenyl-1,4,5,6-tetrahydropyrazolo[3,4-*e*]pyrrolo[3,4-*g*]indolizine (**9**).

To polyphosphoric acid (6.0 g) pre-heated at 90° the oxalyl derivative **8** (0.6 g, 0.0017 mole) was added in small portions. The mixture was stirred at 90° for 1 hour, cooled to room temperature and treated with 100 ml of water. Extraction with ethyl acetate, followed by the usual workup of the combined organic solution furnished a solid residue, which was purified by column chromatography (silica gel-chloroform) to give 410 mg (76%) of 4,6-dioxo-1-phenyl-1,4,5,6-tetrahydropyrazolo[3,4-*e*]pyrrolo[3,4-*g*]indolizine **9**, mp 295-297° after recrystallization from acetonitrile; ir: ν NH 3240, ν CO 1760 and 1730 cm^{-1}; pmr (DMSO-d_6): δ 6.8-6.9 (m, 2H, pyrrole β-protons), 6.95-7.10 (m, 1H, pyrrole α-proton), 7.75 (m, 5H, phenyl), 8.32 (s, 1H, pyrazole proton), 11.1 ppm (m, 1H, NH).

Anal. Calcd. for $C_{17}H_{10}N_4O_2 \cdot 0.5H_2O$: C, 65.58; H, 3.56; N, 17.99. Found: C, 65.42; H, 3.25; N, 18.03.

5-Dimethylaminoethyl-4,6-dioxo-1-phenyl-1,4,5,6-tetrahydropyrazolo[3,4-*e*]pyrrolo[3,4-*g*]indolizine (**4**).

A mixture of 4,6-dioxo-1-phenyl-1,4,5,6-tetrahydropyrazolo[3,4-*e*]pyrrolo[3,4-*g*]indolizine **9** (2.1 g, 0.0068 mole), anhydrous potassium carbonate (1.87 g, 0.014 mole) and dimethylaminoethyl chloride hydrochloride (0.98 g, 0.0068 mole) was heated at 70° with stirring for 20 hours. After cooling, the mixture was poured onto crushed ice and the precipitate which formed was taken up into ethyl acetate. The organic solution was washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude residue was purified by column chromatography (alumina-chloroform). Removal of the solvent from the central eluates gave 1.1 g (44%) of 5-dimethylaminoethyl-4,6-dioxo-1-phenyl-1,4,5,6-tetrahydropyrazolo[3,4-*e*]pyrrolo[3,4-*g*]indolizine **4**, mp 165-166° after recrystallization from benzene-petroleum ether; ir: ν CO 1750 and 1690 cm^{-1}; pmr (deuteriochloroform): δ 2.30 (s, 6H, CH_3), 2.60 (t, J = 7 Hz, 2H, CH_2), 3.80 (t, J = 7 Hz, 2H, CH_2), 6.8-7.0 (m, 2H, pyrrole β-protons), 7.33 (m, 1H, pyrrole α-proton), 7.65 (m, 5H, phenyl), 8.42 ppm (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{21}H_{19}N_5O_2$: C, 67.54; H, 5.13; N, 18.76. Found: C, 67.47; H, 5.10; N, 18.58.

4-Cyano-5-ethoxycarbonyl-1-phenyl-1*H*-pyrazolo[3,4-*e*]indolizine (**10**).

To a solution of the enol **8** (522 mg, 0.0015 mole) in dry benzene (15 ml) phosphorus pentoxide (640 mg, 0.0045 mole) was added and the mixture was refluxed for 2.5 hours. After cooling, the supernatant liquid was decanted and the gummy residue in the flask was washed with benzene. The combined organic solution was washed with a saturated solution of aqueous sodium bicarbonate, then brine, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was column chromatographed on alumina eluting with chloroform to yield 410 mg (83%) of pure 4-cyano-5-ethoxycarbonyl-1-phenyl-1*H*-pyrazolo[3,4-*e*]indolizine **10**, mp 130-133° after recrystallization from benzene-petroleum ether; ir: ν CN 2200, ν COOEt 1710 cm^{-1}; pmr (deuteriochloroform): δ 1.43 (t, 3H, $COOCH_2CH_3$), 4.53 (q, 2H, $COOCH_2CH_3$), 6.8-7.0 (m, 2H, pyrrole β-protons), 7.43 (m, 1H, pyrrole α-proton), 7.60 (s, 5H, phenyl), 8.21 ppm (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{19}H_{14}N_4O_2$: C, 69.08; H, 4.27; N, 16.96. Found: C, 68.87; H, 4.16; N, 17.17.

1-Phenyl-1*H*-pyrazolo[3,4-*e*]indolizine-4,5-dicarboxylic Acid (**11**).

A mixture of 4-cyano-5-ethoxycarbonyl-1-phenyl-1*H*-pyrazolo[3,4-*e*]indolizine **10** (1.98 g, 0.006 mole), 10% aqueous potassium hydroxide (20 ml, 0.036 mole) and 95% ethanol (6 ml) was refluxed for 10 hours. The cooled solution was poured onto crushed ice and acidified by adding concentrated hydrochloric acid. The precipitate solid was taken up into ethyl acetate. The combined extract was washed with brine, dried over anhydrous sodium sulfate and evaporated to provide 1.27 g (66%) of 1-phenyl-1*H*-pyrazolo[3,4-*e*]indolizine-4,5-dicarboxylic acid **11**, mp 285-288° after recrystallization from dimethylformamide-water; ir: ν COOH 1730 and 1700 cm^{-1}; pmr (DMSO-d_6): δ 6.82 (s, 3H, pyrrole protons), 7.72 (s, 5H, phenyl), 8.43 ppm (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{17}H_{11}N_3O_4$: C, 63.55; H, 3.45; N, 13.08. Found: C, 63.35; H, 3.43; N, 13.34.

5-Amino-1-phenyl-1*H*-pyrazolo[3,4-*e*]indolizine (**12**).

A solution of 4-cyanomethyl-1-phenyl-5-(1-pyrryl)pyrazole **7** (600 mg, 0.0024 mole) in concentrated hydrochloric acid (2 ml) was stirred at room temperature for 4 hours, then diluted with water and neutralized by adding solid sodium bicarbonate. Extraction with ethyl acetate, followed by the usual workup of the combined organic solution, afforded a solid residue, which was subjected to column chromatography on alumina (chloroform as eluent) to give 450 mg (76%) of 5-amino-1-phenyl-1*H*-pyrazolo[3,4-*e*]indolizine **12**, mp 162-164° after recrystallization from ethanol; ir: ν NH_2 3200-3400 cm^{-1}; pmr (deuteriochloroform): δ 3.62 (s, 2H, NH_2, disappeared with deuterium oxide), 6.22 (s, 1H, H-4), 6.4-6.6 (m, 2H, pyrrole β-protons), 6.82 (m, 1H, pyrrole α-proton), 7.52 (s, 5H, phenyl), 7.80 ppm (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{15}H_{12}N_4$: C, 72.56; H, 4.89; N, 22.57. Found: C, 72.51; H, 4.78; N, 22.71.

Ethyl 1-Phenyl-5-(1-pyrryl)pyrazol-4-acetate (**15**).

A solution of 1-phenyl-5-(1-pyrryl)pyrazol-4-acetic acid **14** [11] (21.4 g, 0.08 mole) in absolute ethanol (200 ml) containing 96% sulfuric acid (5 ml) was refluxed while stirring overnight. The solution was concentrated under reduced pressure, then poured onto crushed ice and basified with solid sodium bicarbonate. The organic product was isolated by extraction with methylene chloride and the separated layer was washed with brine, dried over anhydrous sodium sulfate and evaporated to dryness. Ethyl 1-phenyl-5-(1-pyrryl)pyrazol-4-acetate **15** was obtained in 95% yield as a yellowish oil, homogeneous by tlc (alumina-benzene); ir: ν COOEt 1745 cm^{-1}.

Anal. Calcd. for $C_{17}H_{17}N_3O_2$: C, 69.13; H, 5.80; N, 14.23. Found: C, 68.98; H, 5.78; N, 14.11.

Ethyl α-Ethoxyoxalyl-1-phenyl-5-(1-pyrryl)pyrazol-4-acetate (**16**).

This compound was prepared in 90% yield as reported for derivative **8** starting from **15**, mp 105-107° after recrystallization from ethanol; ir: ν COOEt 1740, ν CO 1660 cm^{-1}.

Anal. Calcd. for $C_{21}H_{21}N_3O_5$: C, 63.79; H, 5.35; N, 10.63. Found: C, 63.61; H, 5.29; N, 10.50.

Diethyl 1-Phenyl-1*H*-pyrazolo[3,4-*e*]indolizine-4,5-dicarboxylate (**17**).

Prepared from **16** in 72% yield following the procedure reported for **10**, mp 86-89° after recrystallization from benzene-petroleum ether; ir: ν COOEt 1730 and 1710 cm^{-1}; pmr (deuteriochloroform): δ 1.44 (2t, 6H, $COCH_2CH_3$), 4.50 (2q, 4H, $COOCH_2CH_3$), 6.7-7.0 (m, 3H, pyrrole protons), 7.60 (s, 5H, phenyl), 8.47 ppm (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.14. Found: C, 66.52; H, 5.02; N, 10.96.

4,5-Bis-(Hydroxymethyl)-1-phenyl-1*H*-pyrazolo[3,4-*e*]indolizine (**18**).

To a stirred and cooled (0-5°) suspension of lithium aluminum hydride (1.14 g, 0.03 mole) in dry diethyl ether (50 ml) a solution of **17** (3.78 g, 0.01 mole) in the same solvent was added dropwise. After stirring for 1 hour at room temperature, water (3.5 ml) was carefully added and the precipitate which formed was filtered. The solid was extracted with several portions of hot ethyl acetate. The combined organic solution was dried while warm over anhydrous sodium sulfate and evaporated under reduced pressure to afford 1.8 g (61%) of the diol **18** as a powder solid homogeneous by tlc (silica gel-ethyl acetate), mp 182-184° after recrystallization from ethanol; ir: ν OH 3300 cm^{-1}; pmr (DMF-d_7): δ 4.9-5.0 (2s, 4H, CH_2), 6.57-6.83 (m, 3H, pyrrole protons), 7.68 (s, 5H, phenyl), 8.30 ppm (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.32; H, 5.17; N, 14.42.

4,5-Bis-(Isopropylaminocarbonyloxymethyl)-1-phenyl-1*H*-pyrazolo[3,4-*e*]-indolizine (**5**).

To a suspension of the diol **18** (0.5 g, 0.0017 mole) in dry methylene chloride (60 ml) 4-dimethylaminopyridine (0.25 g, 0.002 mole) and isopropylisocyanate (0.29 g, 0.0039 mole) were added and the mixture was refluxed under stirring while more isopropylisocyanate (0.29 g portions) was added at 8 hours intervals until the starting material was no more detectable by tlc (5 days reaction). The cooled reaction mixture was sequentially washed with 1*N* hydrochloric acid, 5% aqueous sodium bicarbonate and brine. The dried (sodium sulfate) solution was evaporated under reduced pressure and the solid residue was purified by passing it through a short alumina column. Elution with chloroform gave 0.73 g (92%) of the biscarbamate **5**, mp 232-233° after recrystallization from ethyl acetate; ir: ν NH 3310, ν CO 1680 cm^{-1}; pmr (trifluoroacetic acid): δ 1.1-1.6 (m, 12H, CH_3), 3.87 (m, 2H, CH), 5.0 (s, 2H, CH_2), 5.73 (s, 2H, CH_2), 6.04 (s, 2H, pyrrole protons), 7.6-8.0 (m, 5H, phenyl), 9.10 ppm (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{25}H_{29}N_5O_4$: C, 64.78; H, 6.31; N, 15.11. Found: C, 64.52; H, 6.41; N, 14.86.

4,5-Bis-(Cyclohexylaminocarbonyloxymethyl)-1-phenyl-1*H*-pyrazolo-[3,4-*e*]indolizine (**6**).

By reacting for 8 days the diol **18** with 4-dimethylaminopyridine and cyclohexylisocyanate following the procedure reported for **5**, the biscarbamate **6** was obtained in quantitative yield as a crude solid after chromatography on a short silica gel column (ethyl acetate as eluent). Pure 4,5-bis-(cyclohexylaminocarbonyloxymethyl)-1-phenyl-1*H*-pyrazolo[3,4-*e*]-indolizine **6** was achieved in 38% yield by recrystallization from ethyl acetate, mp 229-231°; ir: ν NH 3300, ν CO 1680 cm^{-1}; pmr (trifluoroacetic acid): δ 1.2-2.2 (broad signals, 20H, CH_2 of cyclohexyl rings), 3.5 (m, 2H, NH-C*H*), 4.96 (s, 2H, CH_2), 5.70 (s, 2H, CH_2), 6.0 (s, 2H, pyrrole protons), 7.5-7.9 (m, 5H, phenyl), 9.06 ppm (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{31}H_{37}N_5O_4$: C, 68.48; H, 6.86; N, 12.88. Found: C, 68.74; H, 6.52; N, 12.92.

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