

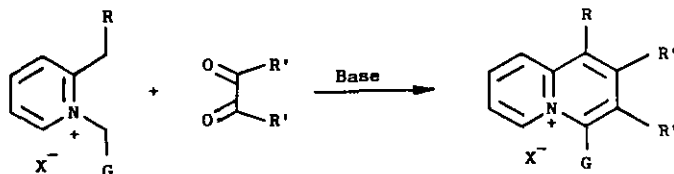
NEW APPLICATIONS OF WESTPHAL CONDENSATION. SYNTHESIS
OF NEW [2.3.3]CYCLAZINONES

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Abstract- Two different types of [2.3.3]cyclazinone isomers were obtained by methods based on the Westphal condensation. 2,6-Dialkylpyridinium salts were condensed with 1,2-acenaphtenequinone to produce [2.3.3]cyclazin-1-one derivatives. By a similar process, a quinolizinium-1-olate was prepared, which was cyclized with DMAD yielding a [2.3.3]cyclazin-6-one derivative.

As the result of our interest in the use of cycloimonium ylides in the synthesis of heterocyclic compounds, we have focussed our attention in the Westphal condensation^{1,2} as one of the simplest methods to produce bicyclic systems with quaternary nitrogen in bridgehead position (Scheme 1). In previous papers³⁻⁶ we have reported how the method can be successfully applied to different azinium salts producing different fused heterocycles.

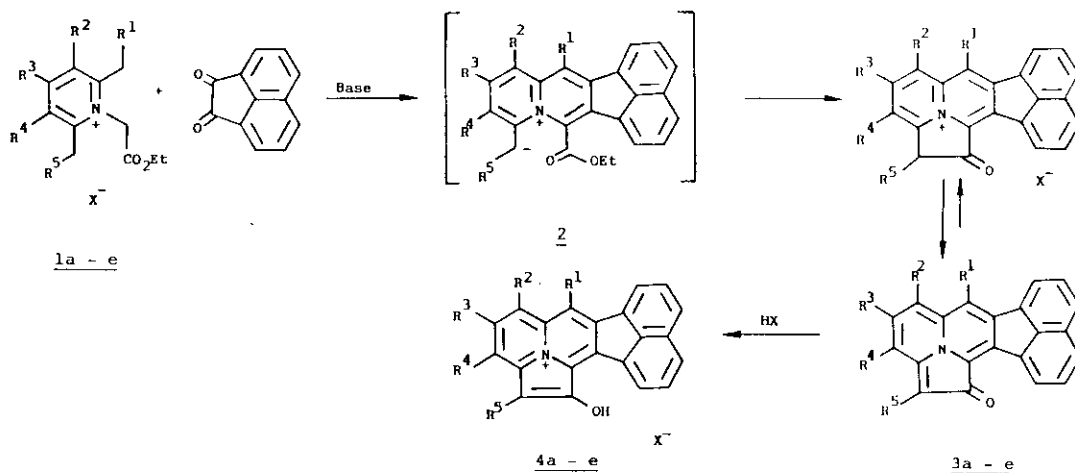


Scheme 1

[2.3.3]Cyclazinones are unsaturated tricyclic molecules held planar by three covalent bonds to an internal nitrogen atom⁷. Leaver and col. have developed two alternative routes to synthesize these ring systems starting with indolizine⁸ and quinolizine derivatives⁹. Recently¹⁰ Miki and col. have used the indolizine approach to obtain several 3- and 5-oxo derivatives.

In the present paper we report our quinolizine approach using the Westphal condensation as the key step in the synthesis of [2.3.3]cyclazin-1- and -6-ones.

When 1-ethoxycarbonylmethyl-2,6-dimethylpyridinium bromide (1a, R¹=R²=R³=R⁴=R⁵=H, Scheme 2) was refluxed with 1,2-acenaphthenequinone in the presence of di-n-butylamine, a deep purple precipitate was formed which did not show any methyl signals in the ¹H-nmr spectrum. The formation of the [2.3.3]cyclazin-1-one derivative 3a can be rationalized as it is represented in Scheme 2. The Westphal condensation between the pyridinium salt and acenaphthenequinone gave the 4-ethoxycarbonyl-6-methylquinolizinium salt which, under reaction conditions, underwent an intramolecular Claisen process, yielding the cyclazinone 3a.



Scheme 2

Other 2,6-dialkylpyridinium salts 1, which can be easily prepared by reaction of the corresponding pyridine derivatives with ethyl bromoacetate underwent similar results, when they were treated with 1,2-acenaphthenequinone in basic medium. This method allows a one step synthesis of [2.3.3]cyclazin-1-one derivatives starting with a monocyclic precursor.

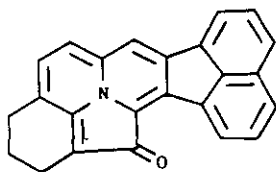
Table 1

Comp.	R ¹	R ²	R ³	R ⁴	R ⁵	X ⁻	Reaction time (h)	Yield (%)	mp (°C)
1a	H	H	H	H	H	Br ^a	2	52	201-202
1b	H	H	CH ₃	H	H	Br ^b	16	80	104-106
1c	H	H	C ₆ H ₅	H	H	Br ^b	4	74	125-126
1d	H	H	H	-(CH ₂) ₃ -		Br ^b	8	51	135-136
1e	-(CH ₂) ₃ -		H	-(CH ₂) ₃ -		BF ₄ ^a	24	40	145-147
1f	OCOCH ₃	H	H	H	H	Br ^a	96 ^c	40	138-140
4a	H	H	H	H	H	Br	3	67	315-317
4b	H	H	CH ₃	H	H	Br	3	67	>360
4c	H	H	C ₆ H ₅	H	H	Br	3.5	61	237-238
4d	H	H	H	-(CH ₂) ₃ -		Br	2.5	41	321-322
4e	-(CH ₂) ₃ -		H	-(CH ₂) ₃ -		Br	3	35	310-312

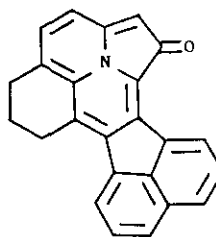
Notes: ^a Acetone as reaction solvent. ^b Acetonitrile as reaction solvent.

^c Room temperature.

It should be noted that by starting with 1d we have only obtained the cyclazinone 3d (Scheme 3) without any traces of the isomer 3d' as the result of a Westphal kinetically-controlled condensation. All cyclazinone derivatives 3 were isolated as hydrobromides 4, for analytical characterization.



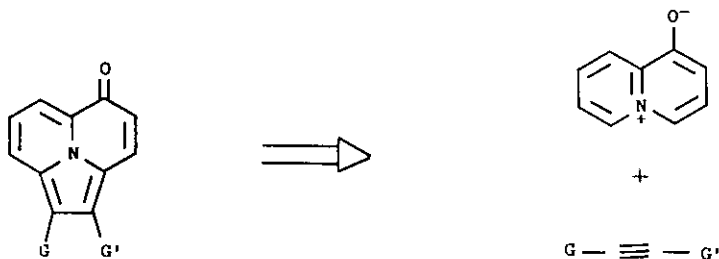
3d



3d'

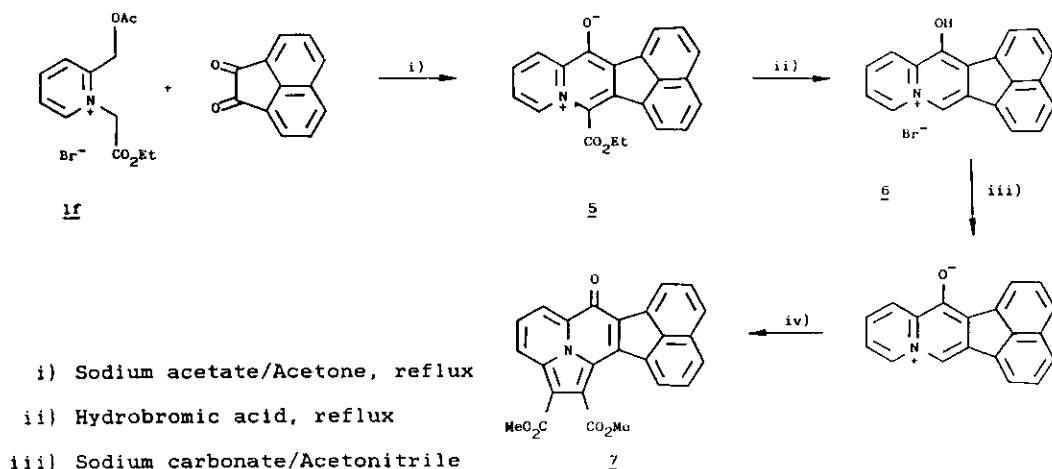
Scheme 3

By using a simple retrosynthetic scheme, we thought that other cyclazinone derivatives, such as [2.3.3]cyclazin-6-ones, could be obtained from a simple quinolizinium precursor, as quinolizinium-1-olate, by means of a 1,3-dipolar cycloaddition process (Scheme 4).



Scheme 4

The only previous reference⁹ for the synthesis of this type of cyclazinone describes its formation as a minor product by nucleophilic attack over a cyclazinium salt. In Scheme 5, it is represented the synthesis of the [2.3.3]cyclazin-6-one derivative 7. The Westphal condensation between 2-acetoxymethylpyridinium bromide 1f and 1,2-acenaphthenequinone in basic medium of sodium acetate yielded the 4-ethoxycarbonylquinolizinium-1-olate 5 which upon reflux with 40% hydrobromic acid produced 6 in fairly good yield. Some of these quinolizinium salts have been previously described by Kröhnke,¹¹ but only the 2,3-diphenyl derivative was obtained in good yield. Unfortunately, we could not reproduce their results.



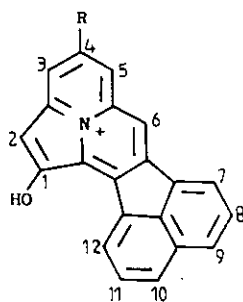
- i) Sodium acetate/Acetone, reflux
- ii) Hydrobromic acid, reflux
- iii) Sodium carbonate/Acetonitrile
- iv) DMAD, reflux

Scheme 5

We have carried out cycloaddition reactions with the conjugated heterocyclic mesomeric betaine derived from 6. The reaction with DMAD (Scheme 5) yielded the [2.3.3]cyclazin-6-one 7 ($G=G' = \text{CO}_2\text{Me}$) in 20% yield, although part of the heterobetaine precursor was recovered at the end of the process (see experimental part). Other dipolarophiles, such as methyl propiolate and phenyl isothiocyanate, have been tested, but in both cases more than 80% of the starting heterobetaine was recovered.

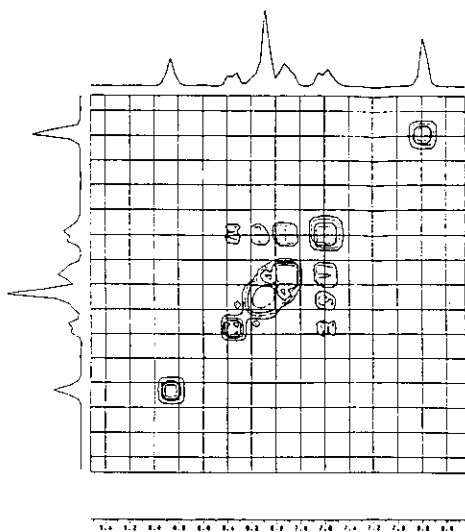
From COSSY experiments, it has been possible to assign all the proton resonances for these derivatives (Table 2). The ^1H -nmr (DMSO- d_6) of 4b shows a clear difference between 7-H and 12-H from the acenaphthene moiety ($\delta = 0.2$ ppm, see table 2) and the high-field doublet ca. $\delta = 8.35$ ppm should be assigned to 12-H due to the proximity of the hydroxyl group. The other protons from this part of the molecule appear as a distorted triplet (ca. $\delta = 7.68$ ppm) for 8-H and 11-H, and two overlapped doublets (7.97 and 8.01 ppm) for 9-H and 10-H. 2-H and 6-H resonances appear as two singlets at 7.12 and 9.27 ppm and finally, 3-H and 5-H from the pyridinium moiety, appear as a broad singlet ca. $\delta = 8.09$ ppm. Similar features can be observed for the other 4 derivatives.

Table 2

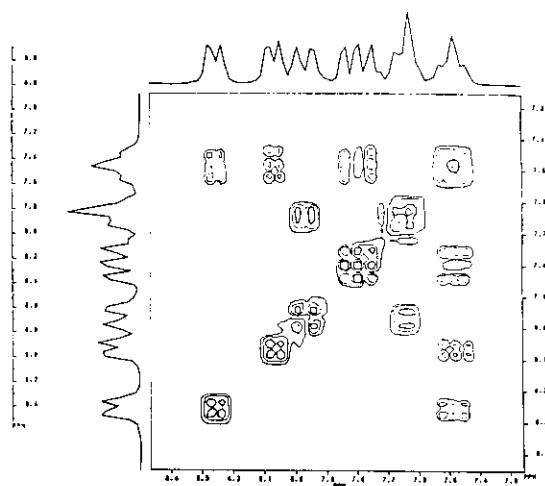


4

R	^1H -Nmr (δ ppm)											Other ones
	2-H	3-H	5-H	6-H	7-H	8-H	9-H	10-H	11-H	12-H		
CH_3	6.79	8.09	8.09	8.87	8.15	7.56	7.97-7.89	7.56	8.35	2.74	(CH_3)	
C_6H_5	6.81	8.60	8.59	8.91	8.07	7.45	7.84-7.75	7.45	8.25	7.95-7.98	($\text{H}_{2',6'}$)	
										7.63-7.66	($\text{H}_{3',4',5'}$)	



4b



4c

EXPERIMENTAL

Melting points were determined on a Büchi SMP-20 and are uncorrected. Ir spectra were recorded on Perkin-Elmer 700 or 1310 spectrophotometers. ^1H -Nmr spectra were obtained on a Varian FT-80 instrument at 80 MHz and a Bruker AC 200P instrument at 200 MHz using TMS as internal reference. Satisfactory microanalyses were obtained for all new compounds described, within 0.4% error.

General Procedure for Preparation of 4-Substituted 2,6-dialkyl-1-etoxy carbonyl-methylpyridinium Salts (Table 1, Compounds 1).

The pyridine derivative (0.22 mmol) and ethyl bromoacetate (0.2 mmol) were refluxed in the indicated solvent (10 ml) (except with 1f). The isolated salt was crystallized in the solvent mixture cited in Table 1.

1a: mp 201-202°C (lit.⁵ 201-202°C) (ethanol-ethyl acetate); ir γ_{max} (KBr) 1630 ($\text{C}=\text{N}^+=$), 1750 ($\text{C}=\text{O}$) cm^{-1} ; ^1H -nmr (DMSO- d_6) δ 1.30 (3H,t,J=7.0Hz), 2.91 (6H,s), 4.35 (2H,q,J=7.1Hz), 5.75 (2H,s), 8.0-8.7 (3H,m).

1b: mp 104-106°C (ethanol-ethyl acetate); ir γ_{max} (KBr) 1635 ($\text{C}=\text{N}^+=$), 1730 ($\text{C}=\text{O}$) cm^{-1} ; ^1H -nmr (DMSO- d_6) δ 1.31 (3H,t,J=6.9Hz), 2.50 (3H,s), 2.68 (6H,s), 4.22 (2H,q,J=6.9Hz), 5.51 (2H,s), 7.79 (2H,s). (Found: C, 49.79; H, 6.41; N, 4.66. Calcd for $\text{C}_{12}\text{H}_{18}\text{NO}_2\text{Br}$: C, 50.01; H, 6.30; N, 4.86).

1c: mp 125-126°C (acetone-ethyl acetate); ir ν_{\max} (KBr) 1632 (C=N⁺=), 1739 (C=O) cm^{-1} ; $^1\text{H-nmr}$ (DMSO- d_6) δ 1.29 (3H,t,J=6.9Hz), 2.89 (6H,s), 4.30 (2H,q,J=7.0Hz), 5.64 (2H,s), 7.5-7.7 (3H,m), 7.9-8.2 (2H,m), 8.47 (2H,s). (Found: C, 58.08; H, 5.88; N, 4.25. Calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_2\text{Br}$: C, 58.29; H, 5.76; N, 4.00).

1d: mp 135-137°C (ethanol-ether); ir ν_{\max} (KBr) 1595 (C=N⁺=), 1743 (C=O) cm^{-1} ; $^1\text{H-nmr}$ (DMSO- d_6) δ 1.27 (3H,t,J=7.0Hz), 1.6-1.9 (4H,m), 2.77 (3H,s), 2.8-3.2 (4H,m), 4.28 (2H,q,J=7.0Hz), 5.61 (2H,s), 7.93 (1H,d,J=8.2Hz), 8.34 (1H,d,J=8.2Hz). (Found: C, 53.70; H, 6.30; N, 4.54. Calcd for $\text{C}_{14}\text{H}_{20}\text{NO}_2\text{Br}$: C, 53.51; H, 6.42; N, 4.46).

1e: mp 145-147°C (ethanol-ether); ir ν_{\max} (KBr) 1595 (C=N⁺=), 1743 (C=O) cm^{-1} ; $^1\text{H-nmr}$ (DMSO- d_6) δ 1.25 (3H,t,J=6.9Hz), 1.7-1.8 (8H,m), 2.9-3.0 (8H,m), 4.15 (2H,q,J=6.9Hz), 5.49 (2H,s), 8.12 (1H,s). (Found: C, 56.35; H, 6.52; N, 4.05. Calcd for $\text{C}_{17}\text{H}_{24}\text{NO}_2\text{BF}_4$: C, 56.53; H, 6.70; N, 3.88).

1f: mp 138-140°C (acetone); ir ν_{\max} (KBr) 1620 (C=N⁺=), 1740 (C=O) cm^{-1} ; $^1\text{H-nmr}$ (DMSO- d_6) δ 1.30 (3H,t,J=6.9Hz), 2.12 (3H,s), 4.28 (2H,q,J=6.9Hz), 5.62 (2H,s), 5.90 (2H,s), 8.2-8.4 (2H,m), 8.81 (1H,t,J=7.0Hz), 9.30 (1H,d,J=5.8Hz). (Found: C, 45.33; H, 5.12; N, 4.28. Calcd for $\text{C}_{11}\text{H}_{16}\text{NO}_4\text{Br}$: C, 45.30; H, 5.07; N, 4.40).

General Procedure for the Preparation of 1-Hydroxy[2.3.3]cyclazinium Salts
(Table 1, Compounds 4).

The pyridinium salt 1 (2 mmol) and 1,2-acenaphthenequinone (2 mmol) were suspended in a mixture (1:2) of ethanol/acetone (15 ml) and di-n-butylamine (2 mmol) was added. The reaction mixture was refluxed for the time described in Table 1. The suspension was concentrated to dryness and the residue triturated with water. The dark brown solid was filtered, diluted with acetone and was then acidified with 47% hydrobromic acid. Finally the mixture was concentrated to dryness, and the residue was washed with acetone (3x20 ml) and then filtered. Crystallization from the adequate solvent yielded the title compounds in analytical grade.

4a: mp 315-317°C (ethanol-hydrobromic acid); ir ν_{\max} (KBr) 1621 (C=N⁺=) cm^{-1} ; $^1\text{H-nmr}$ (DMSO- d_6) δ 7.12 (1H,s), 7.68 (2H,t,J=6.8Hz), 7.97 (1H,d,J=8.5Hz), 8.01 (1H,d,J=8.5Hz), 8.29 (1H,s,J=7.0Hz), 8.5-8.6 (4H,m), 9.27 (1H,s). (Found: C, 65.74; H, 3.61; N, 3.58. Calcd for $\text{C}_{21}\text{H}_{12}\text{NOBr} \cdot 1/2\text{H}_2\text{O}$: C, 65.80; H, 3.42; N, 3.65).

4b: mp >360°C (ethanol-hydrobromic acid); ir γ_{\max} (KBr) 1627 (C=N⁺=) cm⁻¹; ¹H-nmr (DMSO-d₆) δ 2.74 (3H,s), 6.79 (1H,s), 7.60 (2H,t,J=7.2Hz), 7.91 (1H,d,J=7.7Hz), 7.95 (1H,d,J=7.5Hz), 8.1-8.2 (3H,m), 8.35 (1H,d,J=7.0Hz), 8.87 (1H,s). (Found: C, 64.40; H, 4.17; N, 3.22. Calcd for C₂₂H₁₄NOBr.4/3H₂O: C, 64.08; H, 4.07; N, 3.39).

4c: mp 237-238°C (methanol-hydrobromic acid); ir γ_{\max} (KBr) 1626 (C=N⁺=) cm⁻¹; ¹H-nmr (DMSO-d₆) δ 6.81 (1H,s), 7.48 (2H,t,J=7.2Hz), 7.6-7.7 (3H,m), 7.77 (1H,d,J=8.5Hz), 7.81 (1H,d,8.5Hz), 7.9-8.0 (2H,m), 8.06 (1H,d,J=7.0Hz), 8.26 (1H,d,J=7.1Hz), 8.59 (1H,s), 8.60 (1H,s), 8.91 (1H,s). (Found: C, 71.70; H, 3.88; N, 2.83. Calcd for C₂₇H₁₆NOBr: C, 72.01; H, 3.58; N, 3.11).

4d: mp 321-322°C (acetone-hydrobromic acid); ir γ_{\max} (KBr) 1585 (C=N⁺=) cm⁻¹; ¹H-nmr (DMSO-d₆) δ 2.1-2.2 (2H,m), 2.9-3.1 (2H,m), 3.2-3.3 (2H,m), 7.76 (2H,t,J=7.5Hz), 8.07 (1H,d,J=8.0Hz), 8.11 (1H,d,J=8.0Hz), 8.3-8.4 (2H,m), 8.45 (1H,d,J=8.5Hz), 8.61 (1H,d,J=7.0Hz), 9.16 (1H,s). (Found: C, 65.91; H, 4.18; N, 3.21. Calcd for C₂₄H₁₆NOBr.4/3H₂O: C, 65.76; H, 4.28; N, 3.19).

4e: mp >310-12°C (ethanol-hydrobromic acid); ir γ_{\max} (KBr) 1583 (C=N⁺=) cm⁻¹; ¹H-nmr (DMSO-d₆) δ 1.8-2.0 (4H,m), 2.9-3.3 (8H,m), 7.5-8.4 (7H,m). (Found: C, 71.05; H, 4.30; N, 2.82. Calcd for C₂₇H₂₀NOBr: C, 71.37; H, 4.44; N, 3.08).

8-Ethoxycarbonylacenaphtho[1,2-b]quinolizinium-1-olate 5. Equimolecular amounts (2 mmol) of **1g**, 1,2-acenaphthenequinone, and anhydrous sodium acetate were suspended in acetone. The mixture was refluxed for 3 h. The precipitate was filtered and washed with water (20 ml). Yield 82%; mp 186-188°C (acetone); ir γ_{\max} (KBr) 1586 (C=O), 1710 (C=N⁺=) cm⁻¹; ¹H-nmr (DMSO-d₆) δ 1.43 (3H,t,J=7.0Hz), 4.40 (2H,q,J=7.0Hz), 7.7-8.4 (8H,m), 8.84 (1H,d,J=8.2Hz), 9.12 (1H,d,J=7.1Hz); (Found: C, 77.25; H, 4.50; N, 4.02. Calcd for C₂₂H₁₅NO₃: C, 77.40; H, 4.43; N, 4.10).

1-Hydroxyacenaphtho[1,2-b]quinolizinium bromide 6. The quinolizinium-1-olate **5** (1 mmol) was suspended in 48% hydrobromic acid (10 ml) and refluxed for 6 h. The yellow precipitate formed was isolated by filtration. Yield 83%; mp >250°C (from hydrobromic acid); ir γ_{\max} (KBr) 1638 (C=N⁺=) cm⁻¹; ¹H-nmr (DMSO-d₆) δ 7.8-8.6 (8H,m), 8.78 (1H,d,J=8.8Hz), 9.28 (1H,d,J=6.1Hz), 9.83 (1H,s); (Found: C, 63.80; H, 3.65; N, 3.95. Calcd for C₁₉H₁₂NOBr.1/2H₂O: C, 63.52; H, 3.37; N, 3.90).

Reaction between 1-Hydroxyquinolizinium bromide 6 and DMAD. Equimolecular amounts (2 mmol) of **6** and sodium carbonate were suspended in dry acetonitrile (5 ml) and

DMAD (6 mmol) was added. The reaction mixture was refluxed for 24 h. The solution was filtered, and the solid was transformed into the corresponding bromide by hydrobromic acid treatment. A sample of it resulted identical to 6 by ir and nmr (Yield 60%; mp >250°C). The filtrate was evaporated to dryness, and the residue was chromatographed on alumina. Elution with dichloromethane afforded 1,2-dimethoxycarbonyl-6H-[2.3.3]cyclazin-6-one 7 in 20% yield. mp 74-76°C ; ir ν_{\max} (KBr) 1724 (C=O), 1628 (C=O) cm^{-1} ; ^1H -nmr (DMSO- d_6) δ 3.73 (3H,s), 3.82 (3H,s), 7.2-8.1 (8H,m), 8.40 (1H,d,J=5.6Hz); (Found: C, 73.15; H, 3.50; N, 3.17. Calcd for $\text{C}_{25}\text{H}_{15}\text{NO}_5$: C, 73.34; H, 3.69; N, 3.42).

ACKNOWLEDGEMENTS

The authors wish to thank Comisión Asesora de Investigación Científica Técnica (C.A.I.C.Y.T.) for financial support, and to Dr. J. Ezquerro (Lilly S.A. Madrid) for the assistance in the COSSY experiments.

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Received, 11th August, 1989