Phenylation of the 5,11-Diazaditwistane Nucleus

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Received September 18, 1978

A simple phenylation of the 5,11-diazatetracyclo[$6.2.2.0^{2,7}.0^{4,9}$]dodecane system (5,11-diazaditwistane) is described. Phenylative decarboxylation of 5,11-biscarbethoxy-5,11-diazatetracyclo[$6.2.2.0^{2,7}.0^{4,9}$]dodecane-2,9-dicarboxylic acid (**3**) with lead tetraacetate in benzene affords the 2,9-diphenyl analogue (**4**). Hydrolysis yields 2,9-diphenyl-5,11-diazatetracyclo[$6.2.2.0^{2,7}.0^{4,9}$]dodecane (**5**), whereas lithium aluminum hydride affords the 5,11-dimethyl analogue (**6**).

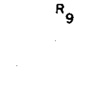
J. Heterocyclic Chem., **16**, 609 (1979).

Recently we reported the synthesis of a substituted member of a new class of heterocyclic compounds, the 5,11-diazaditwistanes (1). This unique ring system possesses a C_2 axis of symmetry, exists in mirror-image forms and contains only twist-boat six-membered rings. During the course of the preliminary studies of 5,11-diazaditwistane chemistry, we discovered a series of new and potent analgesics based on this nucleus (2,3), and more recently we have reported on the synthesis and spectral properties of the parent heterocycle (4).

As part of our continuing study of 5,11-diazaditwistane chemistry, particularly with respect to the analgesic activity of analogs with aryl containing groups at the 2- and 9-bridgehead positions (3), we began seeking methods for the direct attachment of phenyl rings at these positions. Since we have already demonstrated the simple preparation of **1** in quantity (1), transformations from it appeared to be an excellent starting point for our efforts. Treatment of **1** with excess ethyl chloroformate afforded the bis-urethane **2** in good yield, thereby protecting the two basic nitrogens in the system. Controlled hydrolysis of **2** with refluxing hydrochloric acid afforded diacid **3** in 73% yield. Sheldon and Kochi have reviewed a number of transformations of carboxylic acids under oxidative conditions using lead tetraacetate (5). Initially, we planned to convert **3** to the 2,9-dichloro analog followed by arylation *via* organometallic reagents. Treatment of **3** with lead tetraacetate and lithium chloride in benzene according to Kochi (6) afforded a poor yield of the 2,9-dichloro compound. However, spectral examinations of the total neutral product mixture produced by this reaction indicated that phenylation was competitive with chlorination. Kochi has noted phenylation as most often a minor by-product in various lead tetraacetate decarboxylations run in benzene (7). Treatment of **3** with lead tetraacetate in benzene without added lithium chloride proved to be an effective and straighforward method for the diphenylation of **3**, affording **4** in 45% isolated yield. Hydrolysis of **4** with 48% aqueous hydrobromic acid afforded the diamine **5**, whereas, reduction with lithium aluminum hydride afforded the dimethyl analog **6**.

Proton magnetic resonance data for compound **5** are recorded in Table I. The carbon spectrum is summarized in the experimental section. These data confirm the C_2 symmetry of the phenylated product and show that no unexpected rearrangements have taken place. This was not immediately obvious upon inspection of the proton magnetic resonance spectrum of **4**, since it is extremely complex and temperature dependent. This probably reflects varying populations of rotamers due to the interactions of the bulky phenyl and carbethoxyl groups. Such interactions have been previously noted in other highly substituted 5,11-diazaditwistane analogs (8).

Undoubtedly, the facility of the diphenylation of the diazaditwistane nucleus under these conditions results because those processes noted by Kochi (5), which normally compete with phenylation, are rendered much less important by both the bridgehead positions of the carboxyl groups in **3** and their relatively hindered environment. These selective transformations permit both the simple phenylation of the 5,11-diazaditwistane system and control of the substituents on nitrogen. This is particularly important given the unique and rigid nature of the heterocycle and the variety of physiologically active substances which owe their activity to the presence and geometrical relationship of aryl and amino groups. Compounds **5** and **6** did not show any analgesic activity. Further studies in 5,11-diazaditwistane chemistry are continuing.



1, $R_2 = R_9 = CN$; $R_5 = R_{11} = CH_3$

2, $R_2 = R_9 = CN$; $R_5 = R_{11} = COOEt$

3, $R_2 = R_9 = COOH$; $R_5 = R_{11} = COOEt$

4, $R_2 = R_9 = C_6H_5$; $R_5 = R_{11} = COOEt$

5, $R_2 = R_9 = C_6H_5$; $R_5 = R_{11} = H$

6, $R_2 = R_9 = C_6H_5$; $R_5 = R_{11} = CH_3$

0022-152X/79/030609-03$02.25

Table I

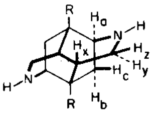
^1H Nmr Spectrum of **5** (a)

Chemical Shift (b)	Multiplicity	J, Hz (Relative Area)	Assignment (c)
1.95	d	$J_{H_bH_c} = 16.5$ (1)	H_c (d)
3.06	q	$J_{H_bH_c} = ?$ (e) $J_{H_aH_b} = 5.0$ (1)	H_b
3.18	s (broad)	- (1)	H_x
3.74	q (broad)	$J_{H_yH_z} = 12.8$ (2)	H_yH_z
4.33	d	$J_{H_aH_b} = 5.0$ (1)	H_a
7.5	multiplet	(5)	C_6H_5

(a) Spectrum taken in deuterium chloride/deuterium oxide with DSS standard at 60 Mhz.

(b) δ, ppm.

(c)



$R = C_6H_5$.

(d) Dihedral angle $H_aC_1C_{10}H_c \sim 90°$, $J_{H_aH_c} \sim 0$.

(e) Part of this pattern was obscured by H_x.

EXPERIMENTAL

5,11-Biscarbethoxy-2,9-dicyano-5,11-tetracyclo[6.2.2.0^{2,7}.0^{4,9}]-dodecane (**2**).

A mixture of 36.0 g. (0.148 mole) of **1** and 125 ml. of ethyl chloroformate was refluxed for 5.5 hours. A small amount of insoluble solid (3.9 g.) was filtered and washed with 2 x 10 ml. of ethyl chloroformate. The filtrates were concentrated under vacuum to a solid mass which was distributed between 200 ml. of methylene chloride and 100 ml. of 2.5*N* hydrochloric acid. The organic layer was washed with 100 ml. of 2.5*N* hydrochloric acid and with 100 ml. of water. It was then taken to dryness and the resulting solid dried under vacuum to yield 38.8 g. (0.108 mole, 73%) of **2**, m.p. 176-180°.

Anal. Calcd. for $C_{18}H_{22}N_4O_4$: C, 60.3; H, 6.1; N, 15.6; M, 358. Found: C, 60.0; H, 6.2; N, 15.5; M, 358.

This material was used without further purification.

5,11-Biscarbethoxy-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane-2,9-dicarboxylic Acid (**3**).

A slurry of 100 g. (0.28 mole) of **2** in 1.0 l. of concentrated hydrochloric acid was refluxed for 6 hours. The resulting insoluble white solid was filtered, dissolved in 200 ml. of 2.5*N* sodium hydroxide, treated with 5 g. of DARCO KB, filtered and acidified at 25-30° with 250 ml. of 2.5*N* hydrochloric acid. The resulting solid was stirred for 24 hours, filtered, washed with water and dried at 100° to constant weight, thus affording 86.3 g. (0.218 mole, 78.5%) of **3** as a white powder, m.p. >300°.

Anal. Calcd. for $C_{18}H_{24}N_2O_8$: C, 54.5; H, 6.1; N, 7.1. Found: C, 54.8; H, 6.2; N, 7.5.

5,11-Biscarbethoxy-2,9-diphenyl-5,11-diazatetracyclo-[6.2.2.0^{2,7}.0^{4,9}]dodecane (**4**).

A mixture of 20.0 g. (0.051 mole) of **3** and 100 g. (0.23 mole) of lead tetraacetate in 500 ml. of benzene was refluxed for 20 hours with vigorous stirring. After cooling, the reaction mixture was added to 2 l. of saturated sodium bicarbonate solution, stirred for 2 hours and filtered through Supercel. After separation, the aqueous layer was washed with 500 ml. of benzene. The combined benzene extracts were taken to dryness at reduced pressure. The solid residue was taken up in 350 ml. of acetone, filtered and concentrated to 300 ml. Cooling produced 10.35 g. of **4** in two crops (0.023 mole, 45%), m.p. 204-207°.

Anal. Calcd. for $C_{20}H_{32}N_2O_4$: C, 73.0; H, 7.0; N, 6.1; M, 460. Found: C, 72.7; H, 7.0; N, 6.2; M, 460.

2,9-Diphenyl-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane (**5**).

A slurry of 10.35 g. (0.023 mmole) of **4** in 250 ml. of 48% aqueous hydrobromic acid was refluxed for 18 hours. The resulting solution was cooled, diluted with 300 ml. of water and made alkaline with 150 ml. of 50% sodium hydroxide at 25°. The resulting solid was filtered, dried and recrystallized from 60 ml. of 2-propanol and 50 ml. of water. Filtration, washing and drying afforded 4.2 g. (0.013 mole, 57%) of **5**, m.p. 191-193°; ^{13}C nmr (deuterium oxide, deuterium chloride, dioxane internal reference): δ ppm 31.5 (d, C_7); 32.3 (t, C_3); 40.2 (s, C_2); 42.2 (t, C_6); 56.8 (d, C_1); 127.4 (d, $C_{2'}$); 129.1 (d, $C_{4'}$), 130.2 (d, $C_{3'}$); 140.0 (s, $C_{1'}$). Multiplicities were observed with off-resonance decoupling.

Anal. Calcd. for $C_{22}H_{24}N_2$: C, 83.5; H, 7.6; N, 8.9; M, 316. Found: C, 83.6; H, 7.8; N, 8.7; M, 316.

5,11-Dimethyl-2,9-diphenyl-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]-dodecane (**6**).

To a stirred slurry of 2.7 g. (71 mmoles) of lithium aluminum hydride in 150 ml. of tetrahydrofuran was added under nitrogen, 6.3 g. (14 mmole) of **4** over a period 5 minutes. The reaction temperature rose to 50°. The mixture was stirred for 24 hours. It was quenched into 2 l. of ice water and extracted with 3 x 100 ml. of methylene chloride. The methylene chloride was dried and taken to dryness to afford 4.4 g. of crude **6**. This was recrystallized from 100 ml. of isopropanol using 0.2 g. of DARCO G60 to afford 3.9 g. (11 mmoles, 83%) of **6**, m.p. 152-154°.

Anal. Calcd. for $C_{24}H_{28}N_2$: C, 83.7; H, 8.2; N, 8.1; M, 344. Found: C, 83.7; H, 8.2; N, 7.9; M, 344.

Acknowledgement.

We wish to thank Dr. A. W. Douglas, Mr. R. A. Reamer and Mr. J. L. Smith for spectral measurements, and Mr. J. P. Gilbert and associates for microanalytical data.

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