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5,11-DIAZADITWISTANE

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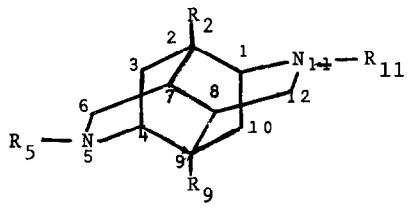
Recently we reported the synthesis of 2,9-dicyano-5,11-dimethyl-5,11-diazatetracyclo[6.2.2.$0^{2,7}$.$0^{4,9}$]dodecane (1), the first analog of the then unknown diazaditwistane series.[1] In a subsequent publication the conversion of 1 to a series of potent analgesics was discussed.[2] As part of our continuing study of 1 and its analogs, we wish to report its conversion to the parent diazaditwistane, 5,11-diaza tetracyclo[6.2.2.$0^{2,7}$.$0^{4,9}$]dodecane (7). In the recent literature the chemistry of simpler analogs, such as ditwistane and azatwistane, has been discussed.[3,4a,b]

Treatment of 1 with excess ethyl chloroformate at reflux resulted in facile demethylation and formation of 2 (72% yield, m.p. 193-195°C).[5] Controlled hydrolysis of 2 with 6N HCl at reflux for 6 hrs. afforded diacid 3 (81%, m.p. 302-304°, decomp.). Decarboxylation of 3 using Br_2/HgO[6] afforded dibromo-bis-urethane 4 (37% m.p. 194-196.5°) along with bromoacid 5 (21%, m.p. 242-245° decomp.). Reduction of 4 with tri-n-butyltin hydride and ethyl acetate at reflux, followed by hydrolysis o the mixture, without isolation of 6, in 48% aqueous HBr afforded 7 as its dihydrobromide salt in 45% overall yield. Alternatively, decarboxylation of 3 with lead tetraacetate in dioxane afforded 6 directly, which when subjected to the HBr hydrolysis afforded 7 in 50% overall yield as its dihydrobromide salt (m.p. > 300).[5] Neutralization of the salt with NaOH, followed by freeze drying and sublimation of the resulting solid, afforded 7 as its free base (m.p. 224-226°). As characteristi of all compounds in this series, 7 displayed an intense molecular ion (m/e 164), an a base peak corresponding to fragmentation to its pyridinium analog, which for 7 corresponds to protonated pyridine (m/e 80).

The NMR data for 7, obtained with a Varian XL-100 spectrometer, are summarized in Table I. The C_2 axis of symmetry, already noted for 1 and its biologically active analogs[1,2], is readily apparent from these data. Further studies with this unique system are continuing and will be reported in the future.



1. $R_2 = R_9 = CN$; $R_5 = R_{11} = CH_3$
2. $R_2 = R_9 = CN$; $R_5 = R_{11} = COOC_2H_5$
3. $R_2 = R_9 = COOH$; $R_5 = R_{11} = COOC_2H_5$
4. $R_2 = R_9 = Br$; $R_5 = R_{11} = COOC_2H_5$
5. $R_2 = Br$; $R_9 = COOH$; $R_5 = R_{11} = COOC_2H_5$
6. $R_2 = R_9 = H$; $R_5 = R_{11} = COOC_2H_5$
7. $R_2 = R_5 = R_9 = R_{11} = H$

TABLE I

NMR Data for 5,11-Diazaditwistane·2HBr

^1HNMR (9.5 mg/0.5 cc D_2O, $(CH_3)_4N^+Br^-$ reference, 3.33 ppm)

δ_H	Mult.	# H's (relative)	Assignment
2.08	t (J = 2.9 hz)	4	3,10-CH_2's
2.27-2.37	m	2	7,8-CH's
2.65-2.82	m*	2	2,9-CH's
3.44-3.77	m**	4	6,12-CH_2's
3.89-3.98	m***	2	1,4-CH's

*Appears as t, J = 6.3 hz, when 3,10-CH_2's decoupled.

** AB part of ABX pattern; J_{AB} = 12.7 hz, $|J_{AX}| + |J_{BX}|$ = 4.7 hz. Unaffected by decoupling of 3,10-CH_2's.

***Appears as d, J = 6.1 hz when 3,10-CH_3's decoupled.

^{13}CNMR (100 mg/0.5 cc D_2O, dioxane reference, 67.4 ppm)

δ_C	Off-resonance Multiplicity	$^1J_{13CH}$(hz)	Assignment
21.7	t	134	$C_{3,10}$
26.9	d	~ 147	$C_{2,9}$
27.7	d	138	$C_{7,8}$
42.2	t	148	$C_{6,12}$
48.4	d	157	$C_{1,4}$

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