Steroidal Dihydropyrazines

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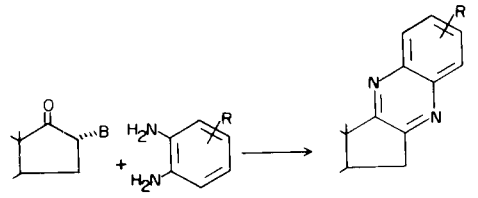
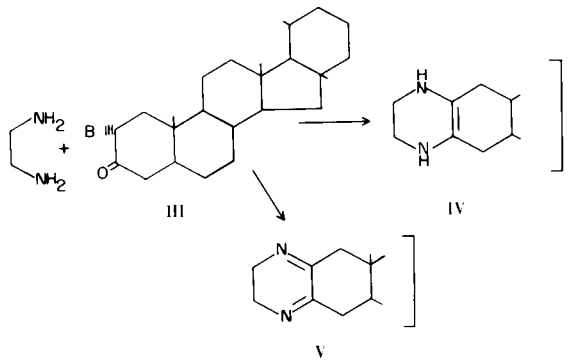
The development of new modified nitrogen steroids with pharmacological interest have been the object of considerable interest in our laboratory (1,2). In a previous communication (3) we have demonstrated that condensation of steroidal α-bromoketones I with substituted *o*-phenylenediamine gives the corresponding substituted quinoxalines II.



I II

A condensation of ethylenediamine with α-diketones is well known to produce dihydropyrazines (4,5). To obtain information on structure-activity relationship in the pyrazinosteroids, we extended Doorenbos and Dorn (6) synthetic work to A and D ring steroids (7).

It has been reported that treatment of 2α-bromo-5α-cholestan-3-one III with ethylenediamine at room temperature resulted in the formation of 5α-cholest-2-ene[2,3-*e*]-tetrahydro-1′,2′,3′,4′-pyrazine IV (6).

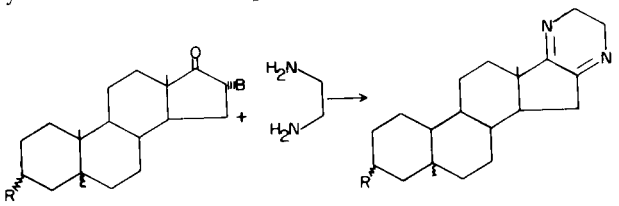


III IV

V

In our hands the 2α-bromocholestanone had given as the main product the 5α-cholestane[2,3-*e*]dihydro-2,3-pyrazine (V). In order to establish the identity of possible intermediates in condensation of the bromoketone with ethylenediamine, we studied the crude final product on tlc with an authentic sample. It was found that the main product was the pyrazinocholestan V. The structure assignment of V was supported by its infrared spectrum which did not indicate NH absorption at 3300 cm^{-1} (8). The C=N band appeared at 1650 and 1610 cm^{-1}.

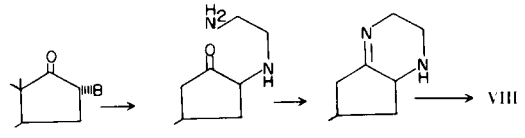
Extention of this reaction to 16α-bromoketones (11-14) with ethylenediamine forms the corresponding dihydropyrazines VIII. The ir spectra of VIII do not show a band



VII VIII

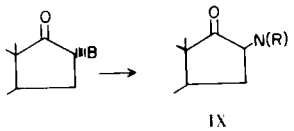
in the region ~ 3300 cm^{-1}, which may be ascribed to the NH stretching vibrations. The nmr spectra are consistent with this assignment; the four protons ($N\text{-}CH_2CH_2\text{-}N$) appeared as a multiplet at τ 6.4. The mass spectra of V and VIIIc (see Experimental) were consistent with the assigned structures.

The following pathway appears most reasonable for the transformation of VII to VIII.



A B

The first step invovles displacement of bromine by ethylenediamine forming the intermediate A as in 16β-aminoketones IX (9,10), followed by ring closure to tetrahydro-



IX

pyrazine B. Compound B, probably was very sensitive to air oxidation and gives final product VIII. Our attempts to

Dihydropyrazines

Compound Number	R	Synthetic Procedure	Yield %	Recrystallization Solvents	M.p. °C	Formula	C	Calcd. % H	N	C	Found % H	N
V	--	A	58	$CH_3COOC_2H_5$	160-161	$C_{29}H_{48}N_2$	82.01	11.40	6.60	81.55	11.57	6.78
VIIIa	H,5αH	A	80	"	199-200	$C_{21}H_{32}N_2$	80.84	10.34	8.82	80.60	10.56	9.02
VIIIb	OH,5αH	A	55	"	204-205	$C_{21}H_{32}N_2O$	76.77	9.81	8.53	76.26	9.64	8.35
VIIIc	$OCOCH_3$,5αH	B	45	CH_3OH	195-196	$C_{23}H_{34}N_2O_2$	74.59	9.18	7.56	74.37	9.32	7.45
VIIId	$OCOCH_3$,Δ⁵	B	30	$CH_3COOC_2H_5$	221-222	$C_{23}H_{32}N_2O_2$	75.00	8.79	7.60	75.21	8.90	7.61
"	"	A	44	CH_3OH	"							
VIIIe	OH,Δ⁵	A	57	$CH_3COOC_2H_5$	209-210	$C_{21}H_{30}N_2O$	77.25	9.27	8.58	77.19	9.21	8.60
VIIIf	OH,5βH	A	50	CH_3OH	214-215	$C_{21}H_{32}N_2O$	76.77	9.81	8.53	76.96	9.83	8.44

isolate an intermediate such as A or B by exposing bromoketone to ethylenediamine under nitrogen in the cold or at reflux were unsuccessful and only starting material and/or dihydropyrazine were obtained.

EXPERIMENTAL

Melting points were determined on a Büchi melting point apparatus and are uncorrected. Ir spectra were recorded with a Perkin-Elmer 521 spectrophotometer in solid phase potassium bromide. Nmr spectra were recorded with a Perkin-Varian Associates A-60 instrument, using deuteriochloroform as a solvent and TMS as the internal standard. Mass spectra were determined on a CEC-110 spectrometer (70 eV) equipped with a direct inlet attachment. Elemental analyses were performed by the Analytical Laboratory of the Chemistry Division, Democritos.

General Synthetic Processes.

Process A.

To a solution of 2.7 mmoles of bromoketone in 30 ml. of 1:1 chloroform-ethanol was added 20 mmoles of distilled ethylenediamine and the mixture was allowed to stay at room temperature for 7 days. The reaction mixture was evaporated under reduced pressure. The remaining residue was dissolved in chloroform and chromatographed on silica gel column. Elution with chloroform-methanol (9.5:0.5) gave the reported dihydropyrazines.

Process B.

To a solution of 5 mmoles of bromoketone in 20 ml. of anhydrous xylene was added 10 mmoles of ethylenediamine and the mixture was refluxed for 36 hours. The solvent was evaporated under reduced pressure and the products were isolated as process A.

The mass spectrum of V m/e (relative intensity), 424 (100%), 423 (15%), 422 (16%), 409 (15%), 326 (15%).

The mass spectrum of VIIIe m/e (relative intensity), 326 (100%), 311 (22%), 293 (14%).

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