Synthesis of New Compounds of the Phencyclidine Family from Aromatic Conjugated Ketones

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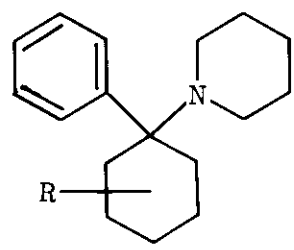
Introduction

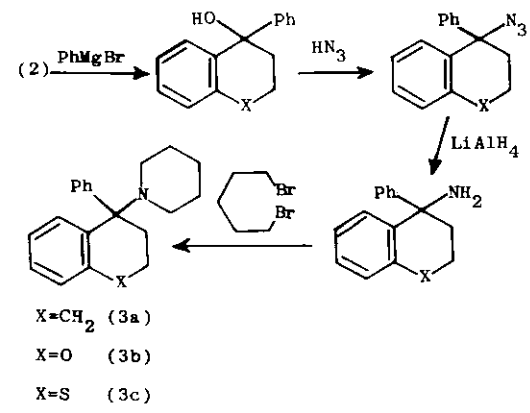
Using 1-tetralone, 4-chromanone, and 4-thiochromanone as starting materials, new compounds of the phencyclidine family were synthesized. These ketones were reacted with C_6H_5Mg Br. The resultant alcohols were treated then with HN_3. The obtained azides were converted to the corresponding primary amines followed by cyclization with 1-5-dibromopentane.

It is well known that 1-(1-phenylcyclohexyl) piperidine (phencyclidine) (1), its derivatives and analogues are biologically active[1]. It is also highly potent and widely abused psychotomimetic drug[2]. Therefore, the preparation, structure study, structure-activity relationship, and rapid identification of these compounds are object of a number of research work [3,4,5]. Up to now only cyclic saturated ketones have been used as starting materials for synthesis of the phencyclidine. On the other hand two other rings (.i.e.aromatic ring and piperidine ring) are needed to the exist in the molecule for its chemically and biologically activity. With this in mind, we though it would be interesting to synthesize a new type of phencyclidine analogues by using conjugated cyclic ketones such as (2). Therefore, our goal was to prepare phencyclidine analogues with an excess aromatic ring and then consider their biological activities. However, we will continue our research on this subject.

The Bruylants[6] reaction was not successful for converting compounds(2) to corresponding phencyclidine analogues. In recent years Geneste and coworkers[7], reported preparation of phencyclidine by azide. Application of this method to our case was successful. Thus, in the first step we prepared the corresponding alcohols by classical method. Treatment of the alcohols with NaN_3 in CCl_3CO_2H-$CHCl_3$ resulted the azides. Hydration of the crude azides without further purification, with $LiAlH_4$ in dry ether yielded primary amines, which then followed by cyclization with 1-5 dibromopentane to give tertiary amines (3a), (3b), and (3c) (Scheme 1). The physical and spectral



(1) (2)



SCHEME-I

characteristic are given in experimental section.

Experimental

Melting points were determined in a Gallenkamp apparatus with capillary tube and are cited uncorrected. I.r. and u.v. spectra were taken using Perkin-Elmer 267 and Varian-Techtron UV visible spectrophotometer model 635. ^1H n.m.r.were determined on a Varian EM-360,TMS as internal standard and $CDCl_3$ as solvent. Mass spectra were determined on a Varian 311 spectrometer.

1-phenyl tetralol,4-phenyl 4-hydroxy chromane and 4-phenyl 4-hydroxy thiochromane were prepared by Grignard reaction reagent as described in litterature[8]. 1-phenyl tetralol, was used without purification in the following reaction, 4-phenyl 4-hydroxy chromane was purified by crystallization m.p. 85-86 °C (from petroleum ether) (litt[9] 101-102 °C from $CHCl_3$). 4-Phenyl 4-hydroxy thiochromane the purified with same way m.p. 84-85 °C (litt [10] 83-84 °C). In all cases, the azides were used without purification, and were confirmed by strong absorbtion at 1100-1110 cm^{-1} for N_3 depend on the case.

Preparation of (3a) [7].

(i)Reaction of 1-Phenyl-tetralol with HN_3

A solution of 1-phenyl tetralol (22,4 gr) in 120 ml of $CHCl_3$ was added dropwise to a stirred mixture of 13 g (0.2 mole) of NaN_3 and 22,5 g (0.2 mole) of CCl_3CO_2H in 100 ml of $CHCl_3$ at -5 °C. The mixture was stirred for 6 hours at O°C. After neutralization with ammonia, the solution was extracted with $CHCl_3$.The chloroform layer was washed with water until neutralized. The solution was dried over Na_2SO_4, and solvent was evaporated, the yield of crude product was 24 g which was used without purification.

(ii)Reaction of azide:

A solution of crude azide (19.9 gr)in 150 ml of dry ether was added to 5.4 g (0.15 mole) of suspension of $LiAlH_4$ in 250 ml of dry ether at O °C, while stirring, the mixture was refluxed for 12 h, then was cooled to -10 °C. A mixture of 50 ml ethyl acetate and 50 ml of ether was added dropwise to the above solution. All the mixture was poured into an icy 20% HCl solution. The aqueous layer was washed 3 time with ether, excess NaOH was added and extracted with ether, the ether layer was washed with watr and dried over $MgSO_4$. The ether was evaporated, 4.077 g of the desired compound was obtained.

(iii) Cyclization of primary amine with 1-5 dibromopentane

3.42 gr of amine with 5,17 g (0.0225 mole) of 1-5 dibromopentane in 50 ml of dry acetone was refluxe for 2 days. The reaction mixture was cooled, 3 g of K_2CO_3 was added and refluxed for 3 days. The solvent was removed and residue was treated with 10% solution of HCl. The aicd layer was washed with ether and neutralized with NaOH, extracted with ether, which is washed with water and dried over $MgSO_4$. After removing the ether at low pressure 3,30 g of the crude product was achieved. The crude product was purified by chromatography over 150 g Alumine (Merck II-III activity), using ether-petroleum ether (1:9)a 1,4 gr. of (3a) (5% calculated on the 1-tetralone) was yielded. An oily visquous with m.p. of chlorhydrate 158-159 °C (from ethanol, THF and petroleum ether). i.r. (neat) 3040, 3000, 2900, 2840, 1995,

1495, 1460, 1380, 1280, 1230, 1180, 1150, 1110, 1070, 980, 770, 750, 730, 700 cm^{-1}. UV (EtOH) λmax (log ε)215 nm (5,06). ^1H n.m.r. ($CDCl_3$) 1, 4(6H), 1,6-2,8 (10H) 6,9 (5H), 7.5 (4H). ms m/e (relative intensity) 291 (63), 290 (40), 263(38), 262 (87), 248 (25),214(39),208(86), 207 (91),206(89) 205(22),192 (13),191 (30), 189 (12), 180 (14), 179 (43), 178 (42), 165 (26), 130 (22), 129 (87),128(44), 127 (18), 117 (12), 116 (13), 115 (30), 103 (13), 92 (38), 91 (100), 89 (12), 87(20), 84(45), 77 (11), 57 (12), 56(21),55(17), 43 (14), 42 (15), 41 (40), 39 (12).

Preparation of (3b)

The same procedure was followed as above. The yield of (3b)was 6% over 4-chromanone. An oily viscous with m.p. of chlorydrate 187-188 °C (solvent as above).i.r. (neat) 3040,2910,2840, 2810,1600,1570,1460,1440,1370,1300, 1280,1250,1170,1150,1120,1070,1030, 970,940,790,760,700 cm^{-1}. UV (EtOH) λ max(log ε) 216 (4,27). ^1H n.m.r. ($CDCl_3$) δ 1,4 (6H) 2,35 (6H)4,2 (2H) 6,5-7,7 (9H).ms m/e (relative intensity) 293 (18),265 (11), 264 (16) 216 (5), 210 (16), 209(100), 208(11), 207(6), 181 (8), 178(6), 131(11),115 (13), 91 (38),86(25),84(8),70(5),69(10),57(8), 56 (37), 55(11),43(21),42(13),41(25), 39(8).

Preparation of (3c).

The same procedure was followed as (3a). The yield was 5% over 4-thichromanone m.p.78-79 °C (from petroleum ether).m.p. of chlorhydrate 166-168 °C (same solvent as (3a). i.r. (KBr), 3020,2880,2800, 2760, 1560, 1540, 1440, 1420, 1250, 1230, 1130, 1100, 1050, 1010, 970, 960, 730, 700, 680 cm^{-1}. UV (EtOH) λmax (logε) 220 nm (4.15). ^1H n.m.r. ($CDCl_3$) δ 1.4 (6H), 2.45 (6H), 3,8(2H), 6,7-7,7 (9H). ms m/e (relative intensity) 309 (36), 281 (16), 280(12), 226(16), 225(65), 224(76), 223 (14), 198 (16), 197 (28), 912 (20),191 (12), 165(10),147 (27), 115 (15),92 (12), 91 (100), 86(67), 84(38), 41(8).

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