6-Aryl-1-azabicyclo[5.4.0]undecanes

M. Nabil Aboul-Enein (1) and J. Sam

Department of Medicinal Chemistry, The University of Mississippi University, Mississippi 38677

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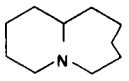
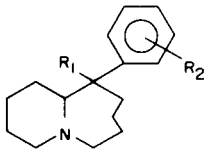
Some 6-aryl-6-hydroxy-1-azabicyclo[5.4.0]undecanes and their esters were synthesized as potential cardiovascular agents and analgetics of the proheptazine type, respectively. Also, 6-aryl-1-azabicyclo[5.4.0]undecanes were prepared as rigid structures related to the phenethylamine CNS stimulants.

Chemical structures with fixed conformations have provided useful information regarding structure-activity relationships (2). The stereochemistry and the biological activity of some quinolizidines have been previously reported (3,4). The interesting results obtained with quinolizidines prompted the investigation of derivatives of the carbocyclic homolog, 1-azabicyclo[5.4.0]undecane (I).



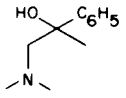
I



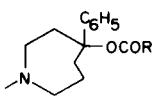
II

Derivatives (II) of I related to: (1) cardiovascular phenylhydroxyalkylamines (III) (*e.g.*, ephedrine) (5); (2) analgetic homopiperidines (IV) (6) and quinolizidines (V) (7); and (3) CNS acting phenethylamines (VI) (*e.g.*, amphetamine) (8), have been synthesized and subjected to pharmacological investigation.

Some information on the sterochemistry of these compounds is provided since few definitive data are available on the conformations of heterocyclic rings containing more than five carbon atoms (9).



III



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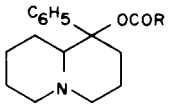
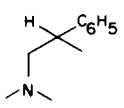
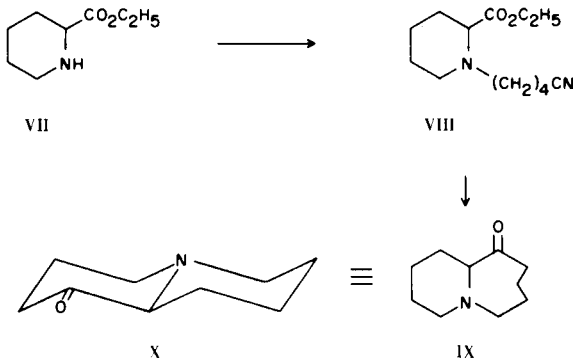


V



VI

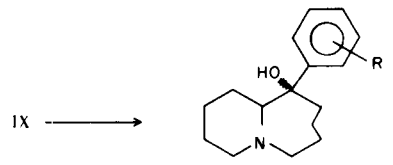
For the preparation of II, 6-keto-1-azabicyclo[5.4.0]-undecane (IX) was used as the starting material. It was prepared according to the method of Leonard and coworkers (10) using Mason's modification in the cyclization step (11).



VII VIII X IX

There is no information available in the literature regarding the stereochemistry of the ketone IX. However, its infrared spectra show strong absorption bands in the 2700-2800 cm^{-1} region (Bohlmann bands (12)), which is consistent with the view that the ketone exists mainly in the *trans*-fused conformation, X (11,12,13,14). The presence of a single component was confirmed by GLC.

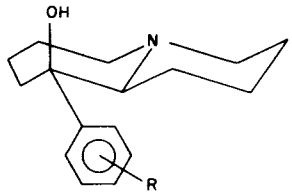
Compounds XI-XVI (Table I) were prepared by the reaction of the appropriate aryl magnesium bromide with 6-keto-1-azabicyclo[5.4.0]undecane (IX). As with the quinolizidines (15) tetrahydrofuran was a necessary solvent for the preparation of the methoxyphenylmagnesium bromides. The 6-(4'-hydroxyphenyl)-6-hydroxy-1-aza-



XI-XVI

TABLE I

6-Aryl-6-hydroxy-1-azabicyclo[5.4.0]undecanes

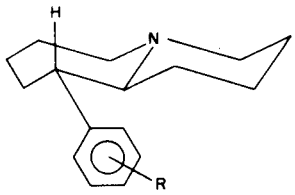


No. (a)	R	M.p.°, C (Recryst. Solv. (b))	Yield %	Molecular Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Intramolecular H-bonding (cm^{-1}) (c)
XI	H	178-9 (E)	97	$C_{22}H_{26}N_4O_8$ (d)	55.69	5.52	11.81	55.89	5.53	11.79	3600 (w) (e), 3440 (s) (e)
XII	2-OCH_3	58-60 (PE)	54	$C_{17}H_{25}NO_2$	74.14	9.15	5.09	74.00	9.32	5.09	3450 (s) (e)
XIII	3-OCH_3	oil (f)	41	$C_{17}H_{25}NO_2$	74.14	9.15	5.09	74.01	9.32	5.08	3450 (s) (e)
XIV	4-OCH_3	oil (f)	45	$C_{17}H_{25}NO_2$	74.14	9.15	5.09	73.82	9.20	5.06	3460 (s) (e)
XV	3,4 $(OCH_3)_2$	224-5	56	$C_{18}H_{28}ClNO_3$ (g)	63.23	8.25	4.09	63.22	8.47	3.92	3450 (s) (e)
XVI	4-OH	172-3 (M-Et)	82	$C_{16}H_{23}NO_2$	73.53	8.87	5.36	73.71	9.19	5.34	3600 (s) (e), 3300 (w) (e)
XVII	4-$OCH_2C_6H_5$	145-7 (C-PE)	43	$C_{23}H_{29}NO_2$	78.60	8.32	3.98	77.95	8.29	4.02	3440 (m) (e)

(a) The infrared and NMR spectra are in agreement with the assigned structures. (b) C = chloroform, E = ethanol, Et = ether, M = methanol, PE = petroleum ether (30-60°). (c) The infrared spectra are taken as liquid films and in Chloroform and Carbon tetrachloride on a Perkin-Elmer Model 257 infrared spectrophotometer. (d) Picrate. (e) S = strong, m = medium, w = weak. (f) Purified by elution chromatography. (g) Hydrochloride.

TABLE II

6-Aryl-1-azabicyclo[5.4.0]undecanes



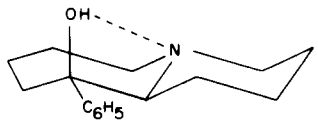
No. (a)	R	B.p.°, C (mm)	Yield %	Molecular Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XX	H	100-2 (0.2)	68	$C_{22}H_{26}N_4O_7$ (b)	57.61	5.72	12.22	57.90	5.79	12.22
XXI	2-OCH_3	120-4 (0.15)	86	$C_{17}H_{25}NO$	78.72	9.71	5.40	78.08	9.83	5.69
XXII	3-OCH_3	140-4 (0.7)	68	$C_{17}H_{25}NO$	78.72	9.71	5.40	78.62	9.84	5.29
XXIII	4-OCH_3	120-4 (0.25) (82-4°) (c)	54	$C_{17}H_{25}NO$	78.72	9.71	5.40	78.75	9.82	5.32
XXIV	3,4-$(OCH_3)_2$	166-8 (0.15)	43	$C_{18}H_{27}NO_2$	74.70	9.40	4.84	75.04	9.56	4.67

(a) The infrared and NMR spectra are in accordance with the assigned structures. (b) Picrate, m.p., 178-179°. (c) M.p., recryst. from pet. ether (30-60°).

bicyclo[5.4.0]undecane (XVI) was obtained by the debenzylation of the 4′-benzyloxy derivative (XVII) with 10% palladium on carbon.

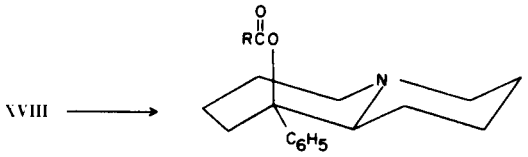
Thin layer chromatography of 6-phenyl-6-hydroxy-1-azabicyclo[5.4.0]undecane (XI) on alumina sheets (Eastman) using: (a) petroleum ether (30-60°): ether (30:70); (b) petroleum ether (30-60°): ether (10:90); and (c) benzene; ethanol (50:50) as the developing systems and iodine vapor as the visualizing agent showed only one single spot. Elution chromatography of XI on Fisher alumina (neutral activity I) using anhydrous ether as eluent, gave fractions which show the same infrared spectra and which give identical picrates (no m.p. depression of mixtures). The infrared spectrum of XI as a liquid film shows one strong band at 3440 cm^{-1}; a weak band at 3600 cm^{-1} and a strong one at 3440 cm^{-1} in carbon tetrachloride which is not changed on dilution is indicative of an intramolecularly hydrogen bonded hydroxyl group situated in the axial position (16,17).

In the aromatic region, there are only two medium bands at 704 and 770 cm^{-1} indicative of an equatorially situated mono-substituted phenyl ring (15). The NMR spectrum of XI shows two families of multiplets in the aromatic region centered at 7.23 δ and 7.56 δ which integrate to three and two protons respectively. This is attributed not only to the interaction of the phenyl group with C_5 and C_8 hydrogens, but also to the anisotropy of the lone pair of electrons on the oxygen atom of the hydroxyl group (18). Dreiding stereo and Framework molecular models illustrate these interactions. The sharp hydroxyl absorption at 3.83 δ is consistent with intramolecular hydrogen bonding (3). On the basis of the data provided above structure XVIII is proposed for alcohol XI. The rings are *trans*-fused; the hydroxyl group possesses the quasi axial and the phenyl nucleus the quasi equatorial positions. This structure exhibits the least steric interactions. A definite conformation could not be exclusively established since the seven membered ring is flexible, more so than the six membered one (19).



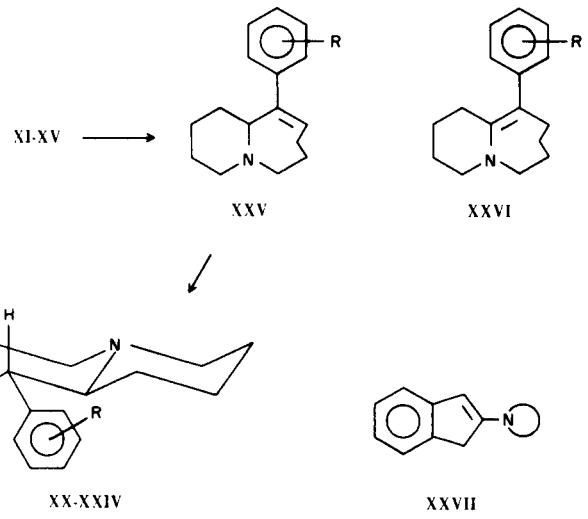
XVIII

The reaction of XVIII with propionyl chloride and with isobutyric anhydride provided esters (XIX) related to proheptazine type analgetics. The unsaturated compounds (XXV) were prepared in nearly quantitative yields from

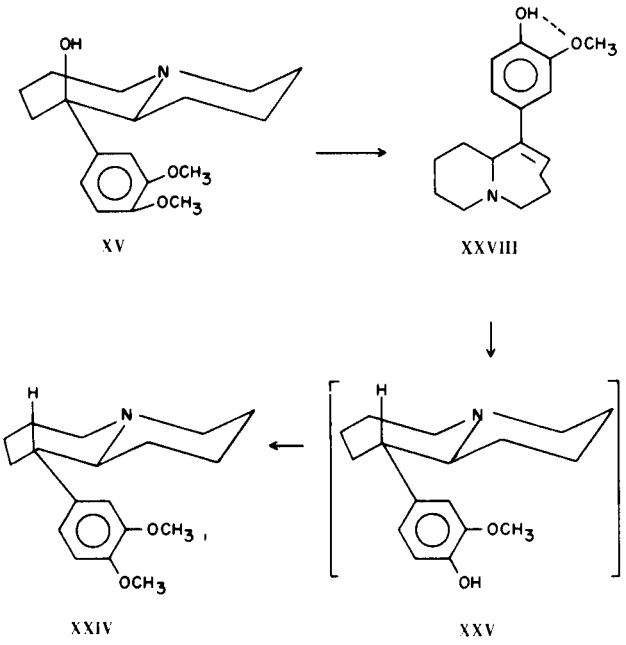


XIXa, R = C_2H_5
b, R = $CH(CH_3)_2$

their respective alcohols (XI-XV) by dehydration with 50% sulfuric acid. The compounds generally were obtained as unstable oils and usually were hydrogenated immediately. The ultraviolet spectra demonstrated that the $\Delta^{6(5)}$ compounds were preferentially formed upon dehydration. The infrared spectra were of little use other than to note the disappearance of the hydroxyl absorption upon dehydration. The UV spectra showed a single absorption maximum near 215 mμ which is evidence that the alternate enamine system (XXVI) was not formed. Blomquist and Moriconi (20) have shown that various enamines of the type indicated by XXVII display two maxima, a broad band at 224-227 mμ and another broad band of greater intensity and longer wave length at 291-303 mμ.



Hydrogenation of XXV was effected in good yields using 10% palladium on carbon. It was observed that during the dehydration of XV, demethylation to XXVIII occurred. The latter produced a strong infrared absorption band at 3555 cm^{-1}, and also was soluble in sodium hydroxide solution. These results are in agreement with observations noted by others (21,22) on related compounds. The hydrogenation of XXVIII followed by methylation provided the corresponding dimethoxy derivative (XXIV).



EXPERIMENTAL (23)

The intermediate δ-[*N*-(2′-ethoxycarbonylpiperidyl)]valeronitrile (VIII) and 6-keto-1-azabicyclo[5.4.0]undecane (IX) were prepared according to procedures described by Leonard and associates (10) and Mason and coworkers (11), respectively.

6-Phenyl-6-hydroxy-1-azabicyclo[5.4.0]undecane XI (Table I).

A solution of 9.2 g. (0.055 mole) of 6-keto-1-azabicyclo[5.4.0]-undecane (IX) in 50 ml. of anhydrous ether was added dropwise over a period of 30 minutes to an ethereal solution of phenylmagnesium bromide (prepared from 8.15 g. (0.335 g.-atom) of magnesium turnings, 51 g. (0.325 mole) of bromobenzene, and 300 ml. of anhydrous ether). The reaction mixture was stirred at room temperature for 1 hour, refluxed gently for 5 hours and further stirred at room temperature for an additional 12 hours. The whitish Grignard complex was maintained at a temperature less than 25° and decomposed by the slow addition of 180 ml. of 15% sodium hydroxide. The ether layer was separated and the precipitate was thrice extracted with 200 ml. portions of ether. The ether extract was washed with three 30 ml. portions of 20% hydrochloric acid. The acidic solution was shaken with ether (3 x 60 ml.), and then basified with 15% sodium hydroxide. An ether extract (3 x 150 ml.) of the precipitate was dried over anhydrous sodium sulfate and evaporated to give 13.1 g. (97%) of yellow viscous oil. An infrared spectrum (liquid film and in carbon tetrachloride) showed the disappearance of the ketonic carbonyl, a strong broad band at 3440 cm^{-1} for the presence of intramolecular H-bonded hydroxyl group and a very weak shoulder at 3600 cm^{-1} for free hydroxyl group (17); the aromatic region showed two bands at 704 cm^{-1} and 770 cm^{-1}. The NMR spectrum (deuteriochloroform) displayed absorptions at 3.83 δ [sharp singlet, 1H (OH)], 7.23 δ (multiplet, 3H aromatic), and 7.56 δ (multiplet, 2H aromatic). Thin-layer chromatograms on alumina sheets using 30:70 petroleum ether (30-60°): ether, 10:90 petroleum ether (30-60°): ether, and 50:50 benzene-ethanol showed a single component to be present.

Three gram portions of XI were dissolved in a small amount of

ether and placed on a 54 x 27 cm. column containing 200 g. of Fisher Grade I neutral alumina. The substance was eluted with anhydrous ether at a flow rate of 4 ml. per minute. The infrared spectra and picrates of all samples were identical. Because of decomposition XI could not be distilled *in vacuo*.

6-Aryl-6-hydroxy-1-azabicyclo[5.4.0]undecanes (XII-XV and XVII) (Table I).

A solution of 0.06 mole of IX in 100 ml. of dry tetrahydrofuran was added dropwise with stirring over a 1 hour period to a 250 ml. tetrahydrofuran solution of Grignard reagent (prepared from 3 g. (0.12 g.-atom) of magnesium turnings and 0.12 mole of the appropriate aryl bromide). The mixture was stirred and refluxed for 24 hours. The Grignard complex thereafter was decomposed by the dropwise addition of 50 ml. of 15% sodium hydroxide and extracted with ether or chloroform (for XVII). The extract was dried over anhydrous magnesium sulfate and evaporated; the product was purified *via* elution chromatography as described for XI.

6-(4′-Hydroxyphenyl)-6-hydroxy-1-azabicyclo[5.4.0]undecane (XVI) (Table I).

A solution of 2.5 g. of XVII in 300 ml. of methanol was hydrogenated in the presence of 0.6 g. of 10% Pd-C for 50-52 hours at room temperature at an initial hydrogen pressure of 48 psi. The mixture was filtered; the filtrate was evaporated to dryness and the residue was recrystallized.

6-Phenyl-6-propionoxy-1-azabicyclo[5.4.0]undecane (XIXa).

To a solution of 11.5 g. (0.046 mole) of XI and 30 g. (0.30 mole) of triethylamine in 200 ml. of dry toluene was added dropwise a solution of 11.5 g. (0.124 mole) of propionyl chloride in 50 ml. of dry toluene. The reaction mixture was stirred under reflux for 6-8 hours. After cooling, the mixture was filtered and the filtrate evaporated under reduced pressure. The residual brown oil was treated with ice cold saturated potassium carbonate solution and extracted with ether (3 x 150 ml.). The extract was dried over anhydrous potassium carbonate and evaporated. The ester was dissolved in petroleum ether (30-60°) and chromatographed on neutral alumina Grade I using petroleum ether (30-60°) as eluent. The chromatographed oil was distilled at 132-135°/0.2 mm to give 3.5 g. (25%) of the ester. A carbonyl band at 1735 cm^{-1} appears in the infrared spectrum (liq. film).

Anal. Calcd. for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.46; H, 9.05; N, 4.69.

6-Phenyl-6-isobutyryloxy-1-azabicyclo[5.4.0]undecane (XIXb)

A solution of 4.7 g. (0.019 mole) of XI and 40 ml. of isobutyric anhydride in 60 ml. of dry pyridine was refluxed for 6 days. After cooling, the reaction mixture was poured on crushed ice and saturated with solid sodium carbonate. An ether extract (3 x 200 ml.) of the separated dark oil was dried over anhydrous sodium sulfate and evaporated. The residual oil was distilled at 130-135°/0.1 mm to give 2.6 g. (41%) of the ester. A strong carbonyl band at 1728 cm^{-1} is present in the infrared (liq. film) spectrum.

Anal. Calcd. for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.39; H, 9.42; N, 4.60.

6-Aryl-1-azabicyclo[5.4.0]undeca-6(5)-ene (XXV).

A solution of 0.02 mole of the appropriate alcohol (XI-XV) in 14 ml. of 50% sulfuric acid was heated under reflux at 125-130° for 1.5 hours. The solution was cooled to 0° and treated with an excess of 15% sodium hydroxide; with XV 10% sodium carbonate was utilized. An ether extract (3 x 100 ml.) of the precipitated oil was dried over anhydrous magnesium sulfate and evaporated to give a nearly quantitative yield of product. Hydroxyl absorption was absent in the infrared spectrum (liq. film). The ultraviolet spectrum showed one maximum at 215 mμ. The product from XV in the infrared region (carbon tetrachloride) showed a strong absorption at 3555 cm^{-1}. This is attributed to the 4-hydroxyl derivative (XXVIII) resulting from monodemethylation (21,22). The dehydrated products (XXV), due to their lability were hydrogenated immediately.

6-Aryl-1-azabicyclo[5.4.0]undecane (XX-XXIII), (Table II).

A solution of the dehydrated product (XXV) in ethanol was hydrogenated in the presence of 10% Pd-C for 48-72 hours at room temperature at an initial pressure of 48 psi. The mixture was filtered; the filtrate was evaporated *in vacuo*, and the residual oil was purified by distillation under reduced pressure.

6-(3′, 4′-Dimethoxyphenyl)-1-azabicyclo[5.4.0]undecane (XXIV). (Table II).

The methylation procedure described by Skaletzky and coworkers (24) was utilized. A mixture of 6.5 g. of crude XXV (prepared as described above for XX) and 1.2 g. of 50% sodium hydride dispersion in mineral oil in 60 ml. of dry DMF was stirred for 15 minutes at room temperature and then cooled at 0-5°. A solution of 4.4 g. of methyl *p*-toluenesulfonate in 5 ml. of DMF was added over a period of 5 minutes. The mixture was stirred for 45 minutes at 0-10°, and then for 48 hours at room temperature. The mixture was evaporated under reduced pressure; the residue was treated with 150 ml. of water and extracted with ether (3 x 100 ml.). The ether solution was extracted with 20% hydrochloric acid (3 x 30 ml.). The acidic solution was basified with 15% sodium hydroxide and extracted with ether (3 x 100 ml.). The extract was dried over anhydrous magnesium sulfate and evaporated to give 5.8 g. of brown oil which was purified by elution chromatography on Fisher neutral alumina Grade I using anhydrous ether as the eluent. The resulting yellow oil was distilled at 166-168°/0.15 mm to give 3 g. of product (43% based on XV). Hydroxyl absorption was absent in the infrared spectrum (carbon tetrachloride).

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(1) This work was supported in part during a tenure of a Mississippi Heart Association Fellowship (M.N.N.) and in part by Grant No. MH 16973 from the U. S. Public Health Service, Bethesda, Maryland.

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