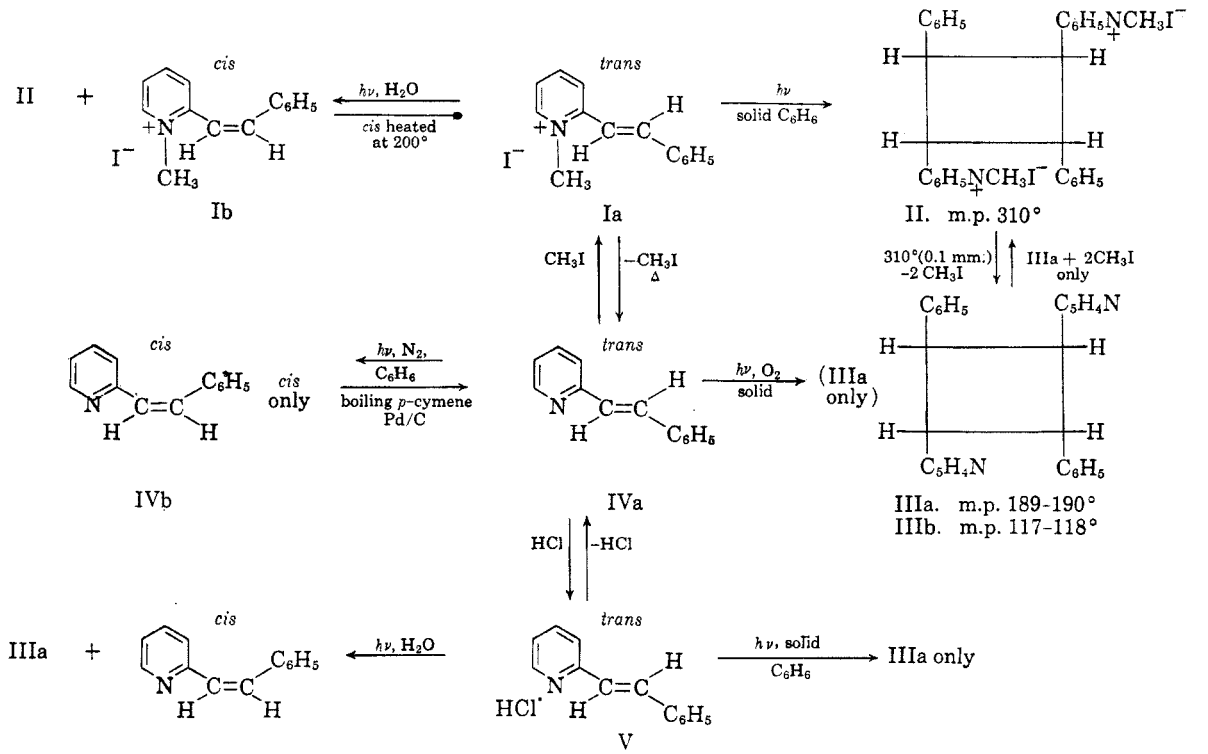


solid (Ib), melting at 181–184° (λ_{max} 325; ϵ 7000). The original mother liquors, when concentrated to 50 ml., gave an additional 2.8 g. of Ib, m.p. 180–183° (λ_{max} 325 mμ; ϵ 10,500).

Anal. Calcd. for $C_{14}H_{14}NI$: C, 52.0; H, 4.35; N, 4.35; I, 39.3. Found: C, 52; H, 4.5; N, 4.2; I, 39.2.

The total yield of Ib was 5.3 g. (28%). The crude solid was extracted again with 50 ml. of boiling water to yield on cooling 1.3 g. of dimer II, m.p. 292° (λ_{max} 272; ϵ 12,700).

Method B: In benzene dispersion. Dimer II. Fifty grams (1.54 moles) of Ia was ball-milled for 16 hr. with 400 ml. of benzene. The suspension was diluted to 4700 ml. and placed in an irradiation flask. After 6 hr. of irradiation, the solids were removed by filtration and dried *in vacuo* at room temperature. The crude solid was recrystallized from 500 ml. of water after a treatment with decolorizing carbon to yield 47 g. (97%) of pure dimer II, melting at 310°.

Isomerization of cis-2-styrylpyridine methiodide (Ib) *to trans-2-styrylpyridine methiodide* (Ia). On standing at room temperature, there was a slow conversion of the *cis* to the *trans* as evidenced by the change of m.p. from 178 to 227°. Pure Ib was first melted at 178°, and the temperature elevated to and held at 200° for 1 or 2 min; the melt resolidified. The temperature was then raised slowly, causing the solid to melt at 225–230° dec. (λ_{max} 340 mμ; ϵ 28,800).

ROCHESTER 4, N. Y.

[CONTRIBUTION FROM THE LABORATORIO DI CHIMICA TERAPEUTICA, ISTITUTO SUPERIORE DI SANITÀ]

Aryldiazaadamantanols. Alkylation of the 9-Position of 1,5-Diphenyl-3,7-diazaadamantan-9-ol

S. CHIAVARELLI AND L. V. FENNOY[1]

Received March 28, 1961

From the reaction of the appropriate alkyllithium with 1,5-diphenyl-3,7-diazaadamantan-9-one a series of nine new 1,5-diphenyl-3,7-diazaadamantan-9-ols has been synthesized for investigation of strychnine-like activity. Attempts to triacetylate the 9-*n*-butyl derivative resulted in dehydration with the formation of an unsaturated bispidine. Reduction of 1,5-diphenyl-3,7-diazaadamantan-9-ol produced unexpectedly 1,5-dicyclohexyl-3,7-dimethylbispidin-9-ol.

The discovery[2] that 1,5-diphenyl-3,7-diazaadamantan-9-ol (III) (1757 I.S.) has strychnine-like activity has caused interest in other structures of this type. Chiavarelli and Settimj[3] prepared 1,5-diphenyl-3,7-diazaadamantan-9-one (I) by the Mannich reaction and reduced it with lithium aluminum hydride to the corresponding diazaadamantanol.

Since the keto group of I could be reduced with

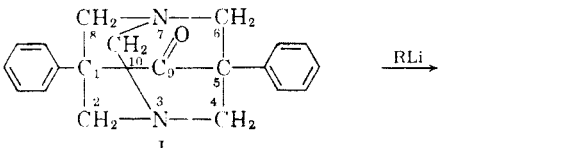
(1) This investigation was carried out during the tenure of a Postdoctoral Fellowship (L. V. F.) from the National Institute of Neurological Diseases and Blindness, United States Public Health Service.

(2) V. G. Longo, B. Silvestrini, and D. Bovet, *Boll. Soc. it. Biol. Sper.*, **39**, 1866 (1958); also see *J. Pharmacol. Exptl. Terap.*, **126**, 41 (1959).

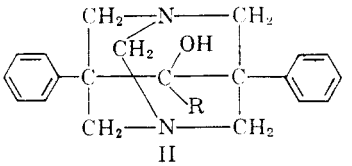
(3) S. Chiavarelli and G. Settimj, *Gazz. chim. ital.*, **88**, 1239 (1958).

lithium aluminum hydride to a secondary alcohol group, it was felt that this keto group would react with Grignard reagents to give a tertiary alcohol group. All attempts to effect reaction of I with different methyl or ethyl Grignard reagents under various conditions failed. In each case there was obtained only the hydrochloride, hydrobromide, or hydroiodide of I. This unreactivity is probably due to the highly hindered keto group.

It is well known that some hindered keto groups which are inert to Grignard reagents will react with alkyllithiums. I does react with alkylithiums[4] to give the desired diazaadamantanols (II) containing a tertiary alcohol group. In each case finely powdered I was rapidly added to the stirred reaction



I



II

III. R = H

mixture of the required alkyllithium in dry ether or petroleum ether. The mixture was then heated to reflux, and the refluxing and stirring were continued as indicated in Table I. The yields were quantitative based on the amount of unchanged I recovered.

Numerous derivatives of I and III have been prepared by Chiavarelli and Settimj[3,5,6] and Chiavarelli, Settimj, and Rabagliati-Canessa.[7] Acetic anhydride reacted with III to give either 1,5-diphenyl-3,7-diacetylbispidin-9-ol or 1,5-diphenyl-3,7,9-triacetylbispidin-9-ol depending upon conditions.[3]

1,5-Diphenyl-9-*n*-butyl-3,7-diazaadamantan-9-ol (II, R = butyl) reacted with acetic anhydride to give 1,5-diphenyl-3,7-diacetylbispindin-9-ol (IV). Attempts to triacetylate (II, R = butyl) caused dehydration, yielding 1,5-diphenyl-9-butylidene-3,7-diacetylbispidine (V). The infrared spectra show the presence of the OH band in IV at 3200 cm.$^{-1}$ This band is not present in V.

Attempts to reduce completely the two phenyl groups of III with ruthenium dioxide and hydrogen did not give the expected 1,5-dicyclohexyl-3,7-diazaadamantan-9-ol, but a new product 1,5-

TABLE I

1,5-DIPHENYL-9-ALKYL-1,3-DIAZAADAMANTAN-9-OLS (II)

I.S. Number	R-Halide Used	Molecular Formula	M.P.[a]	Reflux Time, Hr.	Reaction[b] Solvent	Yield,[c] G.	Recryst.[d] Solvent	Toxicity[e]	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
2703	CH_3—I	$C_{21}H_{24}N_2O$	232–233	2	E	3.4	A-H	12.5	78.71	7.55	8.74	78.84	7.76	8.96
2704	CH_3CH_2—Br	$C_{22}H_{26}N_2O$	215	7	E	5.2	A	20	79.00	7.84	8.37	79.26	8.10	8.51
2705	$CH_3CH_2CH_2$—Cl	$C_{23}H_{28}N_2O$	192–193	38	P	10.6	A-H	20	79.27	8.10	8.04	79.29	8.13	8.16
2666	$CH_3CH_2CH_2CH_2$—Br	$C_{24}H_{30}N_2O$	177–178	96	E	18.0	A	75	79.51	8.36	7.73	79.48	8.48	7.89
2706	$(CH_3)_2CHCH_2$—Cl	$C_{24}H_{30}N_2O$	191	10	P	7.3	A	50	79.51	8.36	7.73	79.35	8.64	7.98
2707	$CH_3(CH_2)_{10}CH_2$—Cl	$C_{32}H_{36}N_2O$	121–122	17	P	11.8	B-H	*f*	80.96	9.77	5.90	80.61	9.86	5.62
2708	C_6H_5—Br	$C_{26}H_{26}N_2O$	253–254	12	E	3.8	A-H	35	81.64	6.85	7.32	81.44	6.88	7.21
2739	α-$C_{10}H_7$—Br	$C_{30}H_{28}N_2O$	255	72	E	20	A	*f*	83.30	6.33	6.48	83.46	6.69	6.63

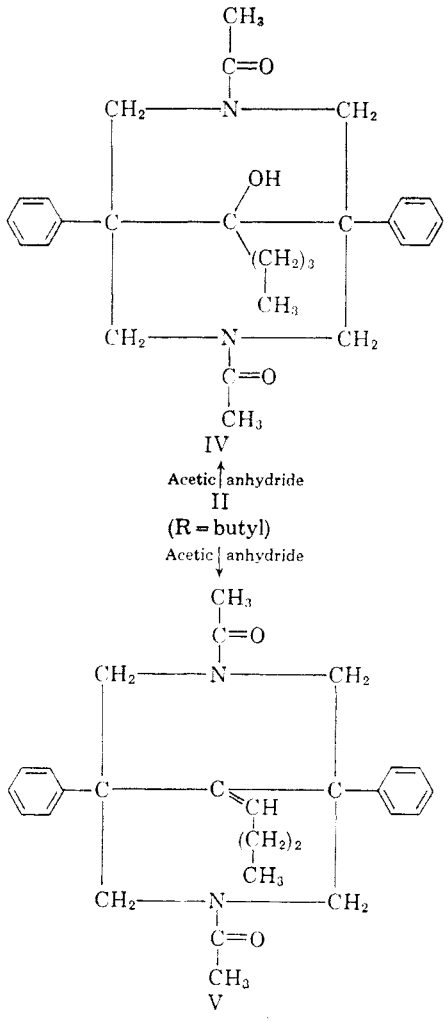
[a] All melting points are uncorrected. [b] P = petroleum ether (b.p. 40–70°), E = ethyl ether. [c] All yields are quantitative based on the amount of diazaadamantanone recovered. [d] A = ethanol B = methanol H = water. [e] Toxicity, mouse LD_{50} i.p. route mg./kg. 1757 I.S., LD_{50} = 1.5 mg./kg. [f] Scarcely soluble.

(4) H. Gilman, E. A. Zoellner, and W. M. Selby, *J. Am. Chem. Soc.*, **55**, 1252 (1933).

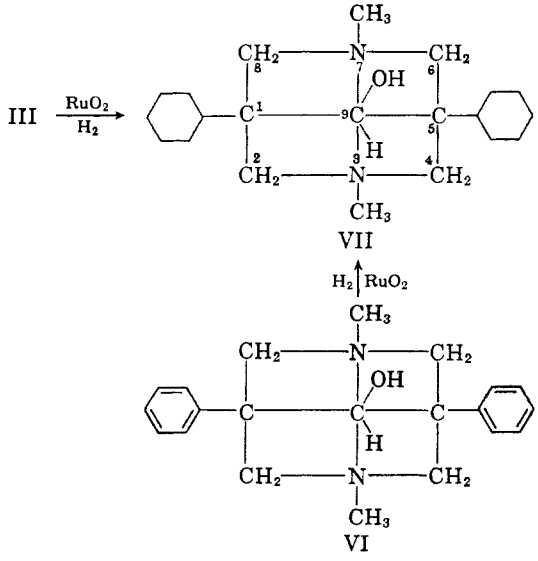
(5) S. Chiavarelli and G. Settimj, *Gazz. chim. ital.*, **88**, 1246 (1958).

(6) S. Chiavarelli and G. Settimj, *Gazz. chim. ital.*, **88**, 1253 (1958).

(7) S. Chiavarelli, G. Settimj, and F. Rabagliati-Canessa, *Gazz. chim. ital.*, **90**, 311 (1960).



dicyclohexyl-3,7-dimethylbispidin-9-ol (VII). VII was also prepared by the reduction of 1,5-diphenyl-3,7-dimethylbispidin-9-ol (VI).



Chiavarelli and Settimj[8] were able to nitrate the phenyl groups of I. Attempts to acetylate the phenyl groups of I with acetyl chloride or acetic anhydride by the Friedel-Crafts reaction, using the method of Noller and Adams[9] were unsuccessful. In both cases only 1,5-diphenyl-3,7-diacetylbispidin-9-one was obtained. Attempts to apply the Friedel-Crafts reaction to this diacetylated bispidone also failed.

Pharmacology. Toxicity tests in various laboratory animals have shown that alkylation of the 9-position of the original molecule (1757 I.S.) decreases the toxicity but leaves unchanged the convulsive strychnine-like action previously reported.[2] The action produced by these derivatives consisted of a first phase of hyperexcitability followed by tonic and tonic-clonic convulsions. The 9-phenyl derivative (2708 I.S.), however, produced a slightly different pattern of intoxication; first observed were fine tremors and then only clonic convulsions.

EXPERIMENTAL

The following directions will serve as a general description of the preparative method for the compounds in Table I. The solvent was either ether or petroleum ether (b.p. 40–70°). In the cases where the yields were less than 100% the dried precipitate was boiled with 100 ml. of ethanol, and the solution decanted hot. This was repeated with three more 100-ml. portions of ethanol. The first two or three fractions contained the diazaadamantanol. The diazaadamantanol solutions were combined and concentrated on a water bath to 100 ml.; the crystals obtained upon cooling were recrystallized from the solvents indicated in Table I.

1,5-Diphenyl-9-n-butyl-3,7-diazaadamantan-9-ol (II. R = *butyl*). To the reaction mixture of *n*-butyllithium [made from 2.75 g. (0.4 g.-atom) of lithium and 27.5 g. (0.2 mole) of *n*-butyl bromide] in 500 ml. of ether, 15.2 g. (0.05 mole) of finely powdered 1,5-diphenyl-3,7-diazaadamantan-9-one was added. The mixture was refluxed and stirred for 96 hr. in an atmosphere of dry oxygen-free nitrogen.[10] After the mixture was cooled to room temperature, it was filtered with suction and the precipitate washed with three 200-ml. portions of hot water. The dried precipitate, m.p. 174–76°, (18 g., 100% yield) was recrystallized three times from 95% ethanol, m.p. 177–178°.

Anal. Calcd. for $C_{24}H_{30}N_2O$: C, 79.51; H, 8.36; N, 7.73. Found: C, 79.48; H, 8.48; N, 7.89.

1,5-Dicyclohexyl-3,7-dimethylbispidin-9-ol (VII). A solution of 6 g. of 1,5-diphenyl-3,7-diazaadamantan-9-ol in 200 ml. of absolute ethanol was hydrogenated with 2 g. of ruthenium dioxide for 2 hr. at 120–150 atm. and 180–185°. The reduction mixture was filtered hot to remove the catalyst. Upon cooling the mixture a small amount of starting material crystallized. This was filtered off, and the solution concentrated to 60 ml., whereupon it deposited 1.8 g. (29% yield) of white crystalline VII, m.p. 197–198°. It was recrystallized once from methanol, m.p. 197–198°.

Anal. Calcd. for $C_{21}H_{38}N_2O$: C, 75.39; H, 11.45; N, 8.37. Found: C, 75.27; H, 11.54; N, 8.32.

Six grams of 1,5-diphenyl-3,7-dimethylbispidin-9-ol was reduced under similar conditions (180–210° and 170 atm.). The same product VII was obtained (3.5 g., 56% yield).

1,5-Diphenyl-9-n-butyl-3,7-diacetylbispidin-9-ol (IV). 1,5-

(8) S. Chiavarelli and G. Settimj, unpublished work.

(9) C. Noller and R. Adams, *J. Am. Chem. Soc.*, **46**, 1889 (1924).

(10) A. Vogel, *Practical Organic Chemistry*, Longmans, Green and Co., London, 1948, p. 182.

Diphenyl-9-*n*-butyl-3,7-diazaadamantan-9-ol, 1 g. (0.0033 mole), was heated on a steam bath for 5 min. with 5 ml. of acetic anhydride. The reaction mixture was allowed to stand for 1 night at room temperature; then 10 ml. of benzene and 20 ml. of ether were added, and the mixture was placed in the deep freeze overnight. The white crystalline material obtained was filtered and recrystallized from ethanol, m.p. 189–90° (1 g., 80% yield).

Anal. Calcd. for $C_{27}H_{34}N_2O_3$: C, 74.62; H, 7.89; N, 6.45. Found: C, 74.45; H, 7.87; N, 6.36.

1,5-Diphenyl-9-butylidene-3,7-diacetylbispidine (V). 1,5-Diphenyl-9-*n*-butyl-3,7-diazaadamantan-9-ol, 3 g. (0.01 mole), was heated on a steam bath for 3 hr. with 15 ml. of acetic anhydride. The acetic anhydride was removed on the water bath under vacuum, leaving a white solid, m.p. 197–198° (3 g., 85% yield). The product was recrystallized twice from ethanol, m.p. 198–199°.

Anal. Calcd. for $C_{27}H_{32}N_2O_2$: C, 77.85; H, 7.74; N, 6.73. Found: C, 77.70; H, 7.79; N, 6.89.

Acknowledgment. We are indebted to Dr. Marzadro for microanalyses, to Dr. L. Baran for toxicity tests, and to Mr. F. Ponti for the infrared spectra.

ROME, ITALY

[CONTRIBUTION FROM MCNEIL LABORATORIES, INC.]

Bicyclic Bases. III. Isomeric 2-Amino-3-phenylnorbornanes[1]

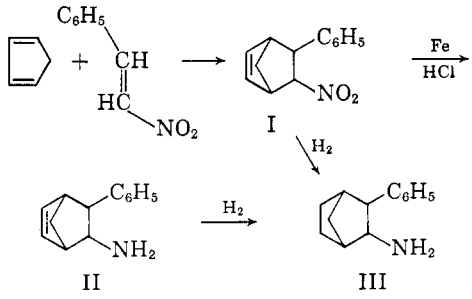
GEORGE I. POOS, JOHN KLEIS, RAYMOND R. WITTEKIND, AND JANET D. ROSENAU

Received July 21, 1961

Proof of the stereochemistry of the known *trans*-2-amino-3-phenylnorbornane is given. Synthesis and structure proof of the other *trans* isomer as well as the *endo-cis* isomer are also accomplished. Attempts are described to obtain the fourth possible isomer with the *exo-cis* configuration.

In connection with our interest in correlating stereochemistry with pharmacological activity, we have investigated several of the isomeric 2-amino-3-phenylnorbornanes.

Our work started with a repetition of the synthesis of 2-amino-3-phenylnorbornene (II) and-norbornane (III) reported by Parham, Hunter, and Hanson[2] from the adduct I[3] of cyclopentadiene and



trans-β-nitrostyrene. These workers had reduced I to the unsaturated amino compound II in about 50% yield with iron and hydrochloric acid. Both I and II were reduced catalytically to the saturated amine III. The amines II and III were characterized by Parham and co-workers as crystalline benzenesulfonamides. However, yields of the benzenesulfonamides were not reported, and no stereochemistry was assigned. We repeated the iron–hydrochloric acid reduction of nitro compound I and obtained unsaturated amine II in 50% yield. The latter was converted in good yield to a single benzenesulfonamide which agreed reasonably well in melting point with that reported.[2] After repeating this portion of the reported work without difficulty, we then set about to (a) prove the stereochemistry of amines II and III; and (b) investigate more critically the nature of the cyclopentadiene-*trans*-β-nitrostyrene adduct I since apparently the work with these compounds had been a side issue with Parham, Hunter, and Hanson.

Reasoning from the "maximum accumulation of unsaturation" of "Alder rule II"[4] in the orientation of *trans*-β-nitrostyrene and cyclopentadiene during their condensation, one would expect adduct I to contain only *trans* adducts and to be predominantly the *endo*-nitro-*exo*-phenyl isomer IX and hence the amines II and III to be the *trans-endo*-amino compounds. An unequivocal synthesis of the saturated amine III proved this to be the case. The cyclopentadiene-*trans*-cinnamoyl chloride adduct IV, known to have the *endo*-acid chloride function and *exo*-phenyl group by interconversion to the acid V and iodolactone VI,[5] was aminated to the unsaturated amide VII. The latter, upon hydrogenation to the saturated amide VIII, gave amine III by Hofmann reaction.

Since the completion of this phase of our work, several reports have appeared on efforts directed towards the proof of the stereochemistry of the amine obtained by reduction of the cyclopentadiene-

(1) Paper II in this series; *J. Org. Chem.*, **26**, 2576 (1961).
(2) W. E. Parham, W. T. Hunter, and R. Hanson, *J. Am. Chem. Soc.*, **73**, 5068 (1951).
(3) C. F. H. Allen, A. Bell, and J. W. Gates, *J. Org. Chem.*, **8**, 373 (1943).
(4) K. Alder and G. Stein, *Angew. Chem.*, **50**, 514 (1937).
(5) C. S. Rondestvedt and C. D. Ver Nooy, *J. Am. Chem. Soc.*, **77**, 4878 (1955).