solvent pair. Except for the tetrabutylammonium iodide, which was dried at 70°, these salts were dried at 80° for 24 hours.

ANALYSIS OF THE REMAINING SALTS

Salt	Theoretical, % halide	Actual, % halide
$(C_2H_5)_4NBr$	38.06	37.98
$(C_2H_5)_4NI$	49.39	49.19
$(C_3H_7)_4NBr$	30.05	29.93
$(C_4H_9)_4NI$	34.39	34.22

Procedure.—The method of saturation and the removal and analysis of samples was the same as reported by Vernon and Goldberg.[2]

Results.—The solubility results given in Table I are the averages of from three to five determinations.

SOLUBILITY OF QUATERNARY AMMONIUM SALTS IN METHANOL AND *n*-BUTANOL AT 25°

Salt	Moles per kg. solution: Methanol	*n*-Butanol
$(CH_3)_4NCl$	3.71 ± 0.025	0.384 ± 0.0005
$(CH_3)_4NBr$	0.269 ± .0012	.0040 ± .0001
$(CH_3)_4NI$	0.0193 ± .00013	
$(C_2H_5)_4NBr$	2.85 ± .0025	.977 ± .0032
$(C_2H_5)_4NI$	0.429 ± .0005	.0076 ± .00016
$(C_3H_7)_4NBr$	2.74 ± .0033	1.72 ± .003
$(C_3H_7)_4NI$	1.83 ± .000	0.195 ± .002
$(C_4H_9)_4NI$	1.95 ± .006	1.04 ± .000

The average deviation of the individual determinations from the mean is no greater than 1% except for the tetramethylammonium bromide and tetraethylammonium iodide where the average deviation is no greater than 3%.

Tetramethylammonium iodide was not run in *n*-butanol because its solubility could not be determined within an experimental error of 5%.

Discussion.—The solubilities of all the salts are greater in methanol, whose dielectric constant is 32.0, than in *n*-butanol with a dielectric constant of 17.8. Within a given quaternary ammonium group the solubilities decrease in the order: chloride, bromide, iodide. The solubility of the iodides in both solvents increases as the quaternary ammonium ion becomes larger. The bromide solubilities in butanol increase with the size of the quaternary ammonium ion but the effect in methanol is not progressive.

(2) G. Goldberg and A. A. Vernon, THIS JOURNAL, **73**, 2845 (1951).

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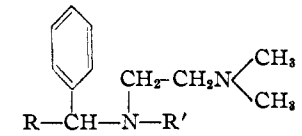
Substituted Tertiary Amines

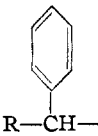
BY FRANK J. VILLANI, MARY S. KING AND DOMENICK PAPA

According to a recent publication of Hall and Burckhalter,[1] the reaction of benzhydryl-2-aminopyridine (IIA) and dimethylaminoethyl chloride in the presence of sodamide yielded β-(dimethylaminoethyl)-2-aminopyridine, instead of the expected N-(β-dimethylaminoethyl)-N-benzhydrylamino-2-pyridine (IA). This observation has prompted us to report some work which was carried out in our

(1) L. A. R. Hall and J. H. Burckhalter, THIS JOURNAL, **73**, 473 (1951).



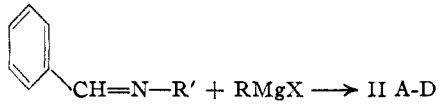
IA, R = phenyl; R′ = 2-pyridyl
IB, R = methyl; R′ = 2-pyridyl
IC, R = phenyl; R′ = phenyl
ID, R = methyl; R′ = methyl



IIA, R = phenyl; R′ = 2-pyridyl
IIB, R = methyl; R′ = 2-pyridyl
IIC, R = phenyl; R′ = phenyl
IID, R = methyl; R′ = phenyl

laboratories several years ago on the synthesis of IA and several related compounds (IB, IC and ID). This work was undertaken as part of a comprehensive program on the synthesis of potential histamine antagonists.[2] An examination of the structure of IA reveals that this compound contains the substituted tertiary nitrogen and benzhydryl moieties characteristic of the clinically effective antihistamines of the ethylenediamine and ethanolamine types, respectively.

The tertiary amine IA was prepared by the alkylation of the secondary amine IIA by adding two moles of sodamide, suspended in toluene, to a mixture of one mole each of IIA and dimethylaminoethyl chloride hydrochloride in toluene. This alkylation procedure differs from that previously described,[1] the latter procedure employing the addition of a benzene solution of dimethylaminoethyl chloride to the sodium salt of the amine. The requisite secondary amines of formula II (A to D) were prepared in good yields by the addition of a large excess of the appropriate Grignard reagent to the corresponding Schiff bases (III) according to the



III

procedure of Moffett and Hoehn.[3] Maximum yields of the secondary amines were obtained when the molar ratio of the Grignard reagent to the Schiff base was at least four to one.

The compounds of formula I were subjected to the previously described pharmacological tests[4] and showed $^1/_{40}$ to $^1/_{100}$ the antihistaminic potency of γ-phenyl-γ-(2-pyridyl)-N,N-dimethylpropylamine.[5]

Experimental

Benzalaniline was prepared in 92% yield by the method of Bigelow and Eatough,[6] m.p. 51–52°.

(2) For the last paper of this series, see D. Papa, N. Sperber and M. Sherlock, *ibid.*, **73**, 1279 (1951).

(3) R. B. Moffet and W. M. Hoehn, *ibid.*, **69**, 1792 (1947).

(4) N. Sperber, D. Papa, E. Schwenk and M. Sherlock, *ibid.*, **71**, 887 (1949).

(5) N. Sperber, D. Papa, E. Schwenk, M. Sherlock and R. Fricano, *ibid.*, **73**, 5752 (1951).

(6) L. A. Bigelow and H. Eatough, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 80.

Benzylidene-2-aminopyridine was prepared by the method of Kirpal and Reiter[7] using 2 moles[8] of 2-aminopyridine to one mole of benzaldehyde, yield 81%, b.p. 184–188° (18 mm.), $n^{21}D$ 1.6564.

Benzhydryl-2-aminopyridine (IIA).—To a cooled, well-stirred phenylmagnesium bromide solution (190 g. of bromobenzene), there was added dropwise over a period of one-half to one hour a solution of 50 g. (0.27 mole) of benzylidene-2-aminopyridine in 50 ml. of anhydrous ether. The reaction mixture was heated on the steam-bath for three hours and then decomposed by the cautious addition of 650 ml. of 10% ammonium chloride solution. The organic layer was separated and the water layer was extracted several times with ether. The combined ethereal solutions were washed with water, dried over anhydrous sodium sulfate and the ether removed by evaporation on the steam-bath. The product was a light yellow solid, m.p. 94–96°. After two recrystallizations with absolute methanol, the product melted at 103–104°; yield 50 g. (70%).

Anal. Calcd. for $C_{18}H_{16}N_2$: N, 10.76. Found: N, 10.44.

The hydrochloride was prepared by saturating an ethereal solution of the base with anhydrous hydrogen chloride. After recrystallization from absolute ethanol–absolute ether, it melted at 192–193°.[9]

α-Phenethyl-2-aminopyridine (IIB) was prepared by a similar procedure in 75% yield from methylmagnesium iodide and benzylidene-2-aminopyridine. After recrystallization from absolute ethanol, the product melted at 91–92°.

Anal. Calcd. for $C_{13}H_{14}N_2$: N, 14.13. Found: N, 13.89.

α-Phenethylaniline (IID),[10] b.p. 180–182° (19 mm.); $n^{28}D$ 1.5955, and benzhydrylaniline (IIC),[11] b.p. 185–188° (1 mm.) were prepared by the same procedure by the action of methylmagnesium bromide and phenylmagnesium bromide, respectively, on benzalaniline.

N-(β-Dimethylaminoethyl)-N-(2-pyridyl)-α-phenethylamine (IB).—A freshly prepared suspension of sodium amide,[12] from 12 g. (0.5 mole) of sodium metal, in 400 ml. of anhydrous toluene was added slowly over a period of 1.5 hours to a vigorously stirred suspension of 39.6 g. (0.2 mole) of α-phenethyl-2-aminopyridine and 33.2 g. of dimethylaminoethyl chloride hydrochloride in 500 ml. of anhydrous toluene. The deep red reaction mixture was slowly heated to reflux and so maintained with stirring for 18 hours. After cooling, 500 ml. of water was added and the toluene solution separated. The water layer, after two ether extractions, was discarded. The combined toluene and ether solutions were extracted several times with dilute hydrochloric acid (10%), the acid solution made strongly basic with concentrated sodium hydroxide solution and extracted with ether. The ether extracts were washed with water, dried over sodium sulfate and distilled, b.p. 149–153° (1 mm.), $n^{25}D$ 1.5730, yield 34 g. (63%).

Anal. Calcd. for $C_{17}H_{23}N_3$: N, 15.97. Found: N, 15.82.

N-(β-Dimethylaminoethyl)-N-(2-pyridyl)-benzhydrylamine (IA) was prepared in a 28% yield by the sodamide alkylation of benzhydryl-2-aminopyridine according to the above procedure, b.p. 195–198° (1 mm.)[13], $n^{22}D$ 1.6141.

Anal. Calcd. for $C_{22}H_{25}N_3$: N, 12.68. Found: N, 12.77.

The following compounds were prepared by a similar alkylation procedure:

N-(β-Dimethylaminoethyl)-N-phenyl-α-phenethylamine (ID), b.p. 205–208° (17 mm.); $n^{27}D$ 1.5709; yield 47%.

Anal. Calcd. for $C_{18}H_{24}N_2$: N, 10.47. Found: N, 10.43.

N-(β-Dimethylaminoethyl)-N-phenylbenzhydrylamine (IC), b.p. 194–195° (1 mm.); $n^{21}D$ 1.6012; yield 51%.

Anal. Calcd. for $C_{23}H_{26}N_2$: N, 8.48. Found: N, 8.55.

(7) A. Kirpal and E. Reiter, *Ber.*, **60**, 666 (1927).

(8) An equimolar ratio of benzaldehyde and 2-aminopyridine under identical conditions gave the product in 50% yield.

(9) Reference 1 reports a melting point of 192–193°.

(10) M. Busch, *Ber.*, **37**, 2691 (1927).

(11) M. Busch and A. Rinck, *ibid.*, **38**, 1761 (1905).

(12) E. M. Hancock and A. C. Cope, *Org. Syntheses*, **25**, 25 (1945).

(13) The distillation was accompanied by a considerable forerun, b.p. 170–195° (1 mm.).

SCHERING CORPORATION
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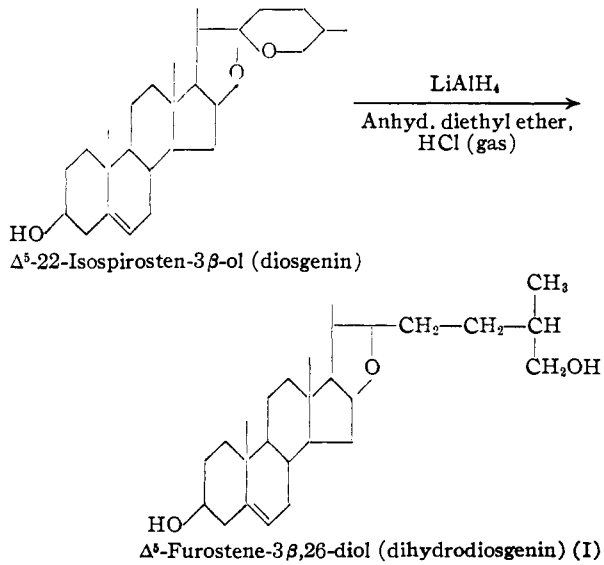
RECEIVED JULY 31, 1951

COMMUNICATIONS TO THE EDITOR

CLEAVAGE OF SAPOGENIN TERMINAL RINGS WITH LITHIUM ALUMINUM HYDRIDE

Sir:

We wish to report a new method for cleaving ring F of steroidal sapogenins.[1] Marker, *et al.*,[2] have reported the preparation of furostane diols (saturated dihydrosapogenins) by reduction of spirostanols and spirostenols, using platinum catalyst in acid solution, but a direct method for the preparation of furostene diols (unsaturated dihydrosapogenins) has not been previously reported. We find that spirostanols and spirostenols are reduced by lithium aluminum hydride ($LiAlH_4$), in the presence of hydrogen chloride gas, to give high yields of the corresponding furostane and furostene diols as illustrated by the reaction shown.



Δ⁵-22-Isospirosten-3β-ol (diosgenin)

Δ⁵-Furostene-3β,26-diol (dihydrodiosgenin) (I)

The sapogenin was dissolved in anhydrous diethyl ether and then the solution was saturated with anhydrous hydrogen chloride gas at 25°. $LiAlH_4$

(1) For nomenclature of steroidal sapogenins see G. Rosenkranz and C. Djerassi, *Nature*, **166**, 104 (1950).

(2) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, THIS JOURNAL, **69**, 2167 (1947).