397. *The Preparation of Mixed Pinacols by Cathodic Reduction. Part II.*[1]

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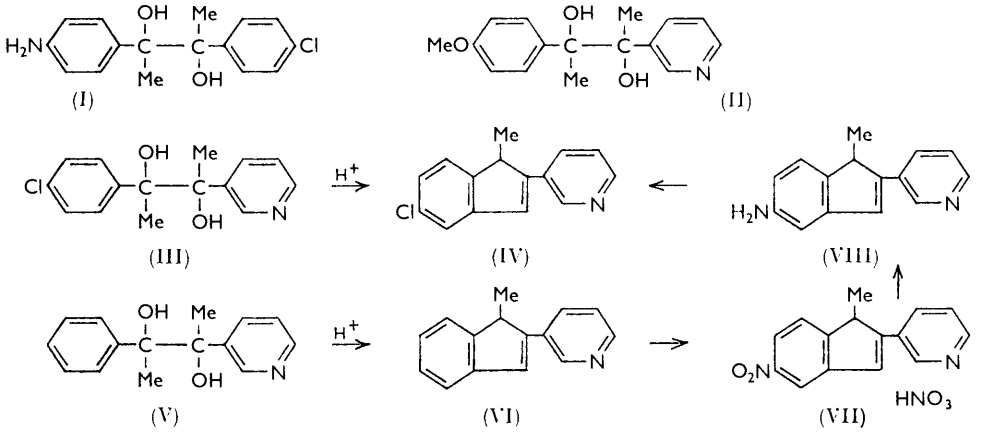
The electrochemical preparation of 2-*p*-aminophenyl-3-*p*-chlorophenyl-, 2-*p*-methoxyphenyl-3-3′-pyridyl-, 2-*p*-chlorophenyl-3-3′-pyridyl-, and 2-phenyl-3-3′-pyridyl-butane-2,3-diol is described. The last two pinacols were converted into their corresponding indenes. The nitration and subsequent reduction of the 1-methyl-2-3′-pyridylindene yielded 5-amino-1-methyl-2-3′-pyridylindene.

The studies to be described were undertaken with the object of preparing some new pinacols which might lead to compounds of therapeutic value. It was known as early as 1950 that the pinacol from 4-aminoacetophenone,[2] on treatment with dilute hydrochloric acid, yielded the biologically active pinacone, 3,3-di-*p*-aminophenylbutan-2-one dihydrochloride [3] (referred to as Amphenone B in biological literature [4]). Since then a

[1] Part I, Allen, Siragusa, and Pierson, *J.*, 1960, 1045.
[2] Allen and Corwin, *J. Amer. Chem. Soc.*, 1950, **72**, 114.
[3] Allen and Corwin, *J. Amer. Chem. Soc.*, 1950, **72**, 114; Bencze and Allen, *J. Org. Chem.*, 1957, **22**, 352.
[4] Chart and Sheppard, *J. Medicin. Pharmaceut. Chem.*, 1959, **1**, 407.

number of pinacones and indenes derived from pinacols have demonstrated this Amphenone-like activity.[5]

The pinacols in this study were obtained by reductive coupling of 4-amino- with 4-chloro-acetophenone, and of acetophenone, 4-chloroacetophenone, and 4-methoxyacetophenone with 3-acetylpyridine. These mixed pinacols were separated from their companion symmetrical pinacols by chromatography on alumina or solvent-distribution. The



various attempts to rearrange 2-*p*-aminophenyl-3-*p*-chlorophenylbutane-2,3-diol (I) and 2-*p*-methoxyphenyl-3-3′-pyridylbutane-2,3-diol (II) to the corresponding pinacones or to dehydrate them to the corresponding indenes resulted in unworkable tars. Although infrared data indicated the presence of both conjugated and unconjugated carbonyl groups after rearrangement of 2-*p*-chlorophenyl- (III) and 2-phenyl-3-3′-pyridylbutane-2,3-diol (V), yields were apparently too small to permit isolation. It was possible, however, to isolate the corresponding indenes (IV and VI) from the reaction mixtures in fairly satisfactory yields.

The indene structure assigned to (IV) was arrived at from ultraviolet spectra and from infrared data in which the band present at 815 cm.$^{-1}$ also indicated a trisubstituted benzene ring. A mechanism previously proposed[6] for the formation of indenes by dehydration of pinacols would place the chloro-group in the 6-position.

It was of further interest to prepare 5-amino-1-methyl-2-3′-pyridylindene (VIII). This was accomplished by nitration of 1-methyl-2-3′-pyridylindene (VI) followed by reduction. The position of the amino-group was verified by its conversion into a chloro-substituent by a Sandmeyer reaction to yield 5-chloro-1-methyl-2-3′-pyridylindene (IV).

Experimental

The electrolysis cells,[7] and the Redoxotrol [8] used for the controlled potential reductions, have been described previously. The reference potentials used in the experiments were obtained from voltammetric curves.

Cathodic Reductions.—The catholyte consisted of equimolar quantities of each ketone. The anolyte was a 40% aqueous potassium carbonate solution. All reactions were performed at the b. p. (82—83°). The other experimental details are outlined in the Table, the reactants being (*a*) 4-amino- (2·7 g.) and 4-chloro-acetophenone (3·09 g.), (*b*) 3-acetylpyridine (9·68 g.) and 4-methoxyacetophenone (12·08 g.), (*c*) 3-acetylpyridine (57·42 g.) and 4-chloroacetophenone (73·28 g.), and (*d*) 3-acetylpyridine (57·42 g.) and acetophenone (57·19 g.), together

[5] Bencze and Allen, *J. Medicin. Pharmaceut. Chem.*, 1959, **1**, 395.
[6] Allen and Corwin, *J. Amer. Chem. Soc.*, 1950, **72**, 114.
[7] Allen and Cohen, *J. Amer. Electrochem. Soc.*, 1959, **106**, 451.
[8] Allen, "Organic Electrode Processes," Chapman & Hall, 1958, pp. 24—28; *Canad. J. Chem.*, 1959, **37**, 257.

with (in order, *a*, *b*, *c*, *d*) potassium acetate 15, 60, 354, 354 g., ethanol 25, 100, 590, 590 ml., and water 17, 68, 402, 402 ml.

Catholyte	(*a*)	(*b*)	(*c*)	(*d*)
Reference potential (v) vs. S. C. E. ...	−1·8	−1·80	−1·84	−2·0
Cathode area (cm.²)	17·2	52·0	112·2	112·2
Initial amperage	6·4	17·0	17·0	17·5
Final amperage	0·2	0·4	2·9	2·4
Initial applied voltage	8·5	19·5	11·2	13·0
Final applied voltage	2·6	3·0	4·0	6·1
Electrolysis time (min.) to current plateau	32	80	283	230
Coulombs passed	2974 (77%)	15,396 (99·7%)	118,000 (128%)	123,900 (135%)
Approx. yield of mixed pinacol based on analytical data obtained on basic fraction	9·1	18·9	30·0	19·2
Yield of product isolated	4·7	2·9	25·8	10·9

Isolation of Pinacols.—(a) 2-p-*Aminophenyl*-3-p-*chlorophenylbutane*-2,3-*diol* (I). The catholyte was evaporated under reduced pressure to remove the alcohol and then acidified with hydrochloric acid. The acidified solution was exhaustively extracted with methylene chloride, made basic with aqueous potassium hydroxide, saturated with potassium chloride, and extracted with methylene chloride. These extracts were dried (Na_2SO_4) and evaporated to dryness. The resultant brown solid was dissolved in benzene (135 ml.) and placed on a neutral alumina column (Woelm; activity 3; 135 g.). The column was eluted with benzene (15 × 135 ml.) and then with 3 : 1 benzene–ether (5 × 135 ml.). The benzene–ether fractions were combined, evaporated to dryness, redissolved in benzene (30 ml.), and rechromatographed on neutral alumina (30 g.). The column was eluted with benzene (25 × 30 ml.). Fractions 11—25 gave a white crystalline material which on recrystallization from cyclohexane gave the pinacol (0·28 g.), m. p. 135—137° (Found: C, 65·9; H, 6·15; N, 4·8. $C_{16}H_{18}ClNO_2$ requires C, 65·9; H, 6·2; N, 4·8%).

(b) 2-p-*Methoxyphenyl*-3-3′-*pyridylbutane*-2,3-*diol* (II). After distillation of the alcohol from the catholyte the remaining mixture of an oil and aqueous fraction was chilled. The oil was separated, dissolved in butyl alcohol, and extracted a number of times with N-hydrochloric acid. The acid extracts were made basic with 2N-potassium hydroxide, saturated with sodium chloride, and extracted with butyl alcohol. These extracts were dried and evaporated to a brown gum which was dissolved in ethanol, filtered to remove salts, and evaporated to a yellow foam. This foam was extracted with refluxing benzene (3 × 200 ml.) for 1½ hr. periods. The residue obtained after evaporation of the benzene was triturated with ether until the insoluble portion had become completely powdery. The ethereal filtrate was evaporated to a yellow gum which was chromatographed in benzene (150 ml.) on neutral alumina (150 g.; activity 3). The column was eluted with benzene (15 × 150 ml.) and with 3 : 1 benzene–ether (20 × 150 ml.). The oil obtained from the benzene–ether fractions was distilled in a short-path still and the fraction of b. p. 162°/0·001 mm. was collected and triturated with pentane to yield pale yellow crystalline pinacol (0·64 g.), m. p. 78—80° (Found: C, 70·6; H, 7·2; N, 5·05. $C_{16}H_{19}NO_3$ requires C, 70·3; H, 7·0; N, 5·1%).

(c) 2-p-*Chloro*-3-3′-*pyridylbutane*-2,3-*diol* (III). The aqueous mixture obtained after distillation of the catholyte was chilled and the aqueous phase decanted from the orange-yellow cake which was then dissolved in methylene chloride (250 ml.). The methylene chloride solution was extracted with N-hydrochloric acid (4 × 300 ml.), and the extracts were made basic with 2N-potassium hydroxide, saturated with sodium chloride, and extracted with methylene chloride (4 × 200 ml.). The methylene chloride solution was dried (Na_2SO_4) and evaporated to a yellow-brown foam.

As there was still present at this stage a small amount of 3-acetylpyridine, the presence of which made isolation of the desired mixed pinacol difficult, it was necessary to remove this ketone by use of a suitable reagent. Therefore, the foam obtained was refluxed and stirred for 1½ hr. in anhydrous ethanol (345 ml.) with anhydrous sodium sulphate (172 g.), Girard's reagent " T " (37·8 g.), and acetic acid (37·8 ml.). The mixture was cooled and poured into water (1625 ml.) containing sodium hydroxide (19 g.) and ice (740 g.). An additional quantity of sodium hydroxide was added if necessary to adjust the solution to pH 8—8·5 and the whole was extracted with methylene chloride. The methylene chloride extracts were combined,

washed well with water, dried, and evaporated to dryness. The residue was extracted with ether (6 × 250 ml.) until the gum which was formed on contact with ether had changed completely to a powder. The combined extracts were washed well with water, dried, and evaporated to dryness. Distillation in a short-path still at 160°/0·001 mm. gave the *pinacol* (34·0 g.), m. p. 88—90° (Found: C, 64·7; H, 6·0; N, 5·0. $C_{15}H_{16}ClNO_2$ requires C, 64·9; H, 5·8; N, 5·0%).

(d) *2-Phenyl-3-3′-pyridylbutane-2,3-diol* (V). The catholyte was treated as described in the previous isolation procedure. The gummy cake obtained was dissolved in a mixture of 2N-hydrochloric acid (250 ml.) and methylene chloride (250 ml.). After separation, the methylene chloride solution was re-extracted with 2N-hydrochloric acid (3 × 100 ml.). The combined acid extracts were filtered and washed with ether. The solution was made basic with 2N-potassium hydroxide, saturated with sodium chloride, and extracted with methylene chloride. The extracts were dried overnight (Na_2SO_4). The pale yellow precipitate (pinacol from 3-acetylpyridine) was filtered off together with the drying agent. The methylene chloride filtrate was evaporated under reduced pressure to a yellow-amber foam.

The ketonic contaminants were removed by dissolving the foam in anhydrous ethanol (140 ml.) which with stirring was refluxed for 1½ hr. with anhydrous sodium sulphate (85 g.), Girard's reagent " T " (20 g.), and acetic acid (20 ml.). The mixture was chilled and poured into water (800 ml.) containing sodium hydroxide (10 g.), sodium chloride (400 g.), and ice (350 g.). The resulting basic mixture was extracted with methylene chloride, and the extracts were washed with water, dried, and evaporated under reduced pressure. The residue obtained was extracted with ether (6 × 250 ml.), and the extracts were washed with water, dried, and evaporated under reduced pressure. Short-path distillation of the residue gave the *pinacol*, b. p. 130—135°/0·001 mm., which, on cooling, was a white hygroscopic powder (12·5 g.), m. p. 118—120° (Found: C, 73·6; H, 7·15; N, 5·9. $C_{15}H_{17}NO_2$ requires C, 74·0; H, 7·0; N, 5·75%).

5-Chloro-1-methyl-2-3′-pyridylindene (IV).—A solution of undistilled pinacol (III) (70 g.) in concentrated hydrochloric acid (1 l.) was refluxed for 36 hr., filtered, chilled, and kept below 20° while the filtrate was made basic with a saturated sodium hydroxide solution. The supernatant liquid was decanted from the gum and extracted with methylene chloride (3 × 600 ml.). These extracts were used to dissolve the gum, then dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure. The residue was exhaustively extracted with ether, and the extracts were combined and evaporated to dryness. The residue on crystallization from anhydrous ethanol gave yellow crystals of the *indene* (18·9 g.), m. p. 99—100° (Found: C, 74·8; H, 5·2; N, 5·7; Cl, 14·6. $C_{15}H_{12}ClN$ requires C, 74·5; H, 5·0; N, 5·8; Cl, 14·7%), $\lambda_{max.}$ 226—227 (ε 5240), 301—306 (ε 11200), 323sh Å (ε 6750).

An additional quantity of indene (10 g.) was obtained by evaporating the ethanol filtrate to dryness and passing the residue in 3 : 1 pentane–benzene (1 l.) through an alumina column (activity 2; 1 kg.). The column was eluted with the pentane–benzene solution (10 × 1 l.). The first 2 fractions were discarded and the subsequent fractions upon evaporation yielded the crystalline indene.

1-Methyl-2-3′-pyridylindene (VI).—The pinacol, 2-phenyl-3-3′-pyridylbutane-2,3-diol (V) (12·5 g.) was refluxed for 48 hr. in concentrated hydrochloric acid (800 ml.). The solution was heated for an additional 15 min. with Norite, filtered, chilled, made basic with sodium hydroxide solution, and extracted a number of times with ether. The dried ether extracts were evaporated to dryness and the residue triturated exhaustively with pentane, which on evaporation followed by short-path distillation (127—132°/0·005 mm.) gave pale yellow solid. Recrystallization from 40% ethanol gave pale yellow crystals of *indene* (4·6 g.), m. p. 59·5—60·5° (Found: C, 86·7; H, 6·3; N, 6·5. $C_{15}H_{13}N$ requires C, 86·9; H, 6·3; N, 6·75%). The *hydrochloride*, made by using dry hydrogen chloride and ether, had m. p. 178·5—180° (Found: C, 73·8; H, 6·0; N, 5·8. $C_{15}H_{14}ClN$ requires C, 73·9; H, 5·8; N, 5·7%).

Undistilled pinacol, of ~95% purity, was also satisfactory for this preparation.

1-Methyl-5-nitro-2-3′-pyridylindene Nitrate (VII).—The undistilled indene (VI) was suitable for this reaction. To the indene (2·95 g.) at 0° was added portionwise, with swirling, concentrated nitric acid (150 ml.). After 2 hr. at 0° the solution was poured with stirring into 2 l. of ice and water and the mixture set aside for ½ hr. The precipitate was collected and recrystallized from 95% ethanol, to yield the yellow *product* (2·16 g.), m. p. 165° (decomp.) (Found: C, 57·4; H, 4·2; N, 13·15. $C_{15}H_{13}N_3O_5$ requires C, 57·1; H, 4·15; N, 13·3%).

5-Amino-1-methyl-2-3′-pyridylindene (VIII).—A mixture of the nitroindene nitrate (VII) (1·93 g.), granular tin (5·8 g.), and 15% hydrochloric acid (570 ml.) was heated with occasional

agitation on a steam-bath for 5 hr. The hot solution was poured into water (500 ml.), heated with Norite, filtered, chilled, made basic with aqueous sodium hydroxide and extracted with ether. Evaporation of the ether gave a semisolid mass which solidified. This was extracted with hot hexane, the hexane extracts being then concentrated and refrigerated, to yield the yellow crystalline *indene* (320 mg.), m. p. 132—134° (Found: C, 81·3; H, 6·5; N, 12·6. $C_{15}H_{14}N_2$ requires C, 81·0; H, 6·3; N, 12·6%).

To a solution of the 5-aminoindene (50 mg.) in concentrated hydrochloric acid (2 ml.) at −5° was added, with stirring during 10 min., a cold solution of sodium nitrite (20 mg.) in water (1 ml.). After an additional 15 minutes' stirring, the diazonium solution was poured into a cold stirred solution of cuprous chloride (30 mg.) in 28% hydrochloric acid (1·5 ml.). After 30 min., the mixture was allowed to warm to room temperature and stirring continued for 3 hr. Finally the stirred mixture was warmed to 70° and the dark red solution then decanted and chilled. The solution was made basic and extracted with ether. The ether extracts were dried and evaporated. The residue was extracted with pentane. Slow evaporation gave crystals, m. p. 98—100°, alone or mixed with 5-chloro-1-methyl-2-3′-pyridylindene. The infrared spectra of the compounds were identical.

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