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234. Pyrazoline Local Anæsthetics. Part I. Derivatives of Benzylidene- and Anisylidene-acetone.

By HUGH B. NISBET.

Derivatives of 1: 5-diphenyl-3- β -dialkylaminoethylpyrazoline and the corresponding 3- β -piperidinoethyl compounds have been shown to possess local anæsthetic properties when tested by the rabbit's cornea and human wheal methods. For the investigation of the influence of substituents in the molecule on the pharmacological properties, a large number of compounds have been synthesised from 1-dialkylamino (or 1-piperidino)-5-phenyl (or p-anisyl)- Δ ⁴-penten-3-one hydrochlorides by conversion into the phenylhydrazones or substituted phenylhydrazones, followed by isomerisation to the pyrazolines. New methods are given for this type of isomerisation.

The general results of the pharmacological examination (reported fully elsewhere) indicate that increase in the size, up to di-*n*-propylamino-, of the dialkylamino-group increases the local anæsthetic potency and to a lesser degree the toxicity. The replacement by p-tolyl or p-ethoxyphenyl of the 1-phenyl radical gives slight increase in activity. The toxicity also is increased in the case of the p-ethoxyphenyl derivative.

NISBET and GRAY (J., 1933, 839) have shown that the phenylhydrazones of β -aminoketones of type (I) can be converted into the isomeric pyrazolines (II):

$$\begin{array}{c} \text{R} \cdot \text{CH:} \text{$$

Considerable difficulty was encountered in several cases in isolating the pyrazoline as the hydrochloride (II), and even the isolation of the base sometimes failed, when glacial acetic acid was used as the isomerising agent (Auwers and Müller, *Ber.*, 1908, **41**, 4232). It has now been found that N-hydrochloric acid or acetic acid diluted with five volumes of water or absolute alcohol readily brings about this change on warming for a short time. As a rule, the pyrazoline hydrochlorides separate readily, or on concentration of the solutions, although in a few cases it is necessary to isolate the pyrazoline as the base.

The phenylhydrazones or substituted phenylhydrazones were formed by the action of substituted hydrazines on unsaturated ketones of the general formula (III), which were themselves obtained by Mannich and Schütz's method (*Arch. Pharm.*, 1927, **265**, 684):

$$\mathbf{R} \cdot \mathbf{CH:} \mathbf{CH} \cdot \mathbf{CO} \cdot \mathbf{CH}_{3} \xrightarrow{\mathbf{CH}_{4}\mathbf{O} + \mathbf{NR'}_{4}, \mathbf{HCl}} \mathbf{R} \cdot \mathbf{CH:} \mathbf{CH} \cdot \mathbf{CO} \cdot \mathbf{CH}_{2} \cdot \mathbf{CH}_{2} \cdot \mathbf{NR'}_{2}, \mathbf{HCl} \quad (\mathbf{III.}) \xrightarrow{\mathbf{R''} \cdot \mathbf{NH} \cdot \mathbf{NH}_{3}} (\mathbf{I.})$$

Benzylideneacetone and formaldehyde condensed with dimethylamine hydrochloride to give a ketone (III; R = Ph, R' = Me); this with phenylhydrazine or p-tolylhydrazine gave hydrazones which were readily isomerised to pyrazolines. The phenylhydrazone, p-tolylhydrazone, and p-ethoxyphenylhydrazone of 1-piperidino-5-phenyl- Δ^4 -penten-3-one hydrochloride (III; R = Ph, $NR'_2 = NC_5H_{10}$) (cf. Mannich and Schütz, *loc. cit.*) have been prepared and converted into the isomeric pyrazolines.

To examine the effect on the anæsthetic activity of the size of the hydrocarbon residue attached to the extranuclear nitrogen atom of the pyrazoline molecule, anisylideneacetone and formaldehyde were condensed with the hydrochlorides of dimethylamine, diethylamine, di-*n*-propylamine, di-*n*-butylamine, piperidine, and dibenzylamine. Unsuccessful attempts were made to carry out the same condensation with dissopropylamine, tetrahydroquinoline, and ethylbenzylamine hydrochlorides. From the unsaturated β -amino-ketones so obtained, by condensation with phenyl- or *p*-tolyl-hydrazine, pyrazolines (II; $R = p-C_6H_4$ ·OMe, $NR'_2 = NMe_2$, NEt_2 , NPr_2 , NBu_2 , or NC_5H_{10} , and R'' = Ph or $p-C_6H_4$ Me) were obtained by isomerisation.

Pharmacological examination of the anæsthetic action of these hydrochlorides by the rabbit's cornea and human wheal methods (Sinha, Thesis, Edinburgh University, 1935; J. Pharm. Exp. Ther., 1936, 57, 199; and paper in preparation) indicated that the

greater the size, up to di-n-propylamino,* of the terminal secondary amino-group, the greater the activity and, to a lesser degree, the greater the toxicity. Two of the more potent anæsthetics amongst these compounds are compared with cocaine in the following table.

	Minimum effective local anæsthetic concentration, %.		Minimum lethal dose intravenously injected
Drug, as hydrochloride.	Human wheal.	Rabbit's cornea.	% of corresponding dose of cocaine).
Cocaine	0.05	0.25	100
l-Phenyl-5- p -anisyl-3- β -piperidinoethylpyrazoline	0.005	0.02	64
1-Phenyl-5-p-anisyl-3-β-di-n-propylaminoethyl-			
pyrazoline	0.002	0.03	85

The introduction of alkyl or alkoxy-groups into the phenyl radical in position 1 (II; R = Ph, $NR'_2 = NC_5H_{10}$, R'' = Ph, $p-C_6H_4Me$, or $p-C_6H_4OEt$) slightly increases the activity (Sinha, loc. cit.). Alkoxy-groups (ethoxy) also increase the toxicity in this case. Attempts were made, therefore, to eliminate the phenyl group in position 1 with the object of decreasing the size of the molecule and, at the same time, probably the toxicity. Condensation of 1-piperidino-5-p-methoxyphenyl- Δ^4 -penten-3-one hydrochloride with hydrazine did not give the desired hydrazone, but a compound, which is probably a ketazine derived from two molecules of the ketone, was isolated as a succinate. The semicarbazone, also, could not be isolated, but an oxime was obtained. The latter was hydrolysed by hydrochloric acid.

EXPERIMENTAL.

 $1-Dimethylamino-5-phenyl-\Delta^4-penten-3-one Hydrochloride.--Benzylideneacetone (14.6 g.)$ and dimethylamine hydrochloride (8.2 g.) were dissolved in absolute alcohol (10 ml.), paraformaldehyde (3.2 g.) added, and the mixture boiled under reflux until it was homogeneous (15-20 mins.). Cooling and scratching caused the separation of a yellow solid, which crystallised from absolute alcohol (30 ml.) in white needles (6 g.), m. p. 157° (Found : Cl, 15.1. C₁₃H₁₇ON,HCl requires Cl, 14.8%). The amino-ketone hydrochloride (3 g.) was dissolved in alcohol (25 ml.; 95%), and phenylhydrazine (1.4 g.) and glacial acetic acid (1.5 ml.) added. After 12 hours yellow needles of the *phenylhydrazone* separated, m. p. 169° after crystallisation from 95% alcohol (Found : C, 69.5; H, 7.3. C₁₉H₂₃N₃,HCl requires C, 67.2; H, 7.3%). The p-tolylhydrazone, prepared by an analogous method, formed bright yellow needles, m. p. $173-175^{\circ}$; it was not very stable.

1: 5-Diphenyl-3-β-dimethylaminoethylpyrazoline Hydrochloride.—The crude phenylhydrazone from 2.7 g. of the above amino-ketone hydrochloride was boiled under reflux with glacial acetic acid (5 ml.) diluted with water (25 ml.). The clear solution obtained after some time was evaporated in a vacuum over sodium hydroxide and anhydrous calcium chloride. The pasty residue solidified when scratched and after two crystallisations from a very small quantity of absolute alcohol at 0° gave white needles, m. p. 176° (Found : Cl, 10.8. C19H23N3,HCl requires Cl, 10.8%).

5-Phenyl-1-p-tolyl-3- β -dimethylaminoethylpyrazoline hydrochloride, similarly obtained (from the p-tolylhydrazone of 1-dimethylamino-5-phenyl- Δ^4 -penten-3-one hydrochloride, 4 g.) and similarly crystallised, formed white needles, which were washed with small quantities of absolute alcohol and dried; m. p. 177-178°. Yield, 1.45 g. (Found : Cl, 10.2. C₂₀H₂₅N₃,HCl requires Cl, 10.3%).

1:5-Diphenyl-**3**- β -piperidinoethylpyrazoline hydrochloride, similarly obtained from the phenylhydrazone of 1-piperidino-5-phenyl- Δ^4 -penten-3-one hydrochloride (Mannich and Schütz, loc. cit.; cf. also Nisbet and Gray, loc. cit.) (5 g.) and twice crystallised from absolute alcohol, formed white needles, m. p. 197° (Found : C, 67.8; H, 8.1; Cl, 9.05; N, 10.3. C₂₂H₂₇N₃,HCl,H₂O requires C, 68.2; H, 7.7; Cl, 9.05; N, 10.9%).

The following compounds were prepared by methods essentially the same as those described above.

I-Piperidino-5-phenyl- Δ^4 -penten-3-one hydrochloride formed a p-tolylhydrazone, yellow

* A di-n-butylamino-derivative has been prepared, but has not yet been subjected to pharmacological tests.

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needles, m. p. 199°, from methyl alcohol (Found : C, 71·7; H, 7·6. $C_{23}H_{39}N_3$,HCl requires C, 72·0; H, 7·65%), and a somewhat unstable *p*-ethoxyphenylhydrazone, yellow needles, m. p. 172°, the isomerisation of which by boiling dilute acetic acid gave 5-*phenyl*-1-p-tolyl-3-*p*-*piperidinoethylpyrazoline hydrochloride*, warty masses, m. p. 212°, from hot water (Found : Cl, 9·2. $C_{23}H_{29}N_3$,HCl requires Cl, 9·25%), and 5-*phenyl*-1-p-*ethoxyphenyl*-3-*p*-*piperidinoethyl*-*yyrazoline hydrochloride*, almost white needles, m. p. 192—193°, from absolute alcohol (Found : Cl, 8·9. $C_{24}H_{31}ON_3$,HCl requires Cl, 8·59%), respectively.

1-Dimethylamino-5-p-anisyl-Δ⁴-penten-3-one hydrochloride (from anisylideneacetone, 17.5 g.) separated from alcohol in colourless needles (17 g.), m. p. 155° (Found : Cl, 13·1; N, 5·4. C₁₄H₁₉O₂N,HCl requires Cl, 13·1; N, 5·2%). The phenylhydrazone formed bright yellow needles, m. p. 135–137° (decomp.), unstable at the ordinary temperature, and the p-tolyl-hydrazone yellow needles, m. p. 170° (Found : N, 11·15. C₂₁H₂₇ON₃,HCl requires N, 11·3%). 1-Phenyl-5-p-anisyl-3-β-dimethylaminoethylpyrazoline hydrochloride crystallised from alcohol in white needles, m. p. 173° (Found : Cl, 9·85. C₂₀H₂₅ON₃,HCl requires Cl, 9·9%), and 1-p-tolyl-5-p-anisyl-3-β-dimethylaminoethylpyrazoline hydrochloride in white needles, m. p. 184° (Found : Cl, 9·5; N, 10·85. C₂₁H₂₇ON₃,HCl requires Cl, 9·5; N, 11·3%).

1-Diethylamino-5-p-anisyl- Δ^4 -penten-3-one hydrochloride (from p-anisylideneacetone, 48 g., and diethylamine hydrochloride, 30·2 g., in absolute alcohol, 27 ml.; paraformaldehyde, 8·8 g.) formed colourless crystals (48 g.), m. p. 146°, from alcohol (Found : Cl, 11·6. C₁₆H₂₃O₂N,HCl requires Cl, 11·9%). The phenylhydrazone formed yellow crystals, m. p. 171°, from alcohol (Found : N, 10·8. C₂₂H₂₉ON₃,HCl requires N, 10·8%).

1-Phenyl-5-p-anisyl-3-β-diethylaminoethylpyrazoline.—The phenylhydrazone of 1-diethylamino-5-p-anisyl- Δ^4 -penten-3-one hydrochloride (22 g.) was heated with glacial acetic acid (66 g.) and water (330 ml.) on the steam-bath for an hour, and the hot solution filtered, made alkaline with caustic soda, and cooled. The precipitated oil was extracted with ether, dried (sodium sulphate), and recovered (18 g.). Extraction with cold light petroleum left a residue of unchanged phenylhydrazone hydrochloride. The oil recovered from the light petroleum was distilled at 2 mm. and crystallised from light petroleum, giving pale yellow needles, m. p. 27° (Found : N, 12·3. C₂₂H₂₉ON₃ requires N, 12·0%). The *tartrate*, obtained as a syrup by treating the base (10 g.) in solution in a small quantity of methyl alcohol with tartaric acid (2 g.) and removing the alcohol on the steam-bath, formed white crystals (8 g.), m. p. 80°, from acetone (Found : C, 67·1; H, 7·5; N, 9·8. C₂₂H₂₉ON₃, $\frac{1}{2}C_4H_6O_6$ requires C, 67·6; H, 7·5; N, 9·8%).

1-Di-n-propylamino-5-p-anisyl- Δ^4 -penten-3-one hydrochloride, obtained from anisylideneacetone (48.1 g.), di-n-propylamine hydrochloride (61.5 g.), and paraformaldehyde (10.5 g.) by heating in alcoholic solution in the usual manner, formed colourless crystals (75 g.), m. p. 150°, from alcoholic acetone (Found : C, 66·4; H, 8·6. C₁₈H₂₇O₂N,HCl requires C, 66·4; H, 8.6%). The phenylhydrazone. Phenylhydrazine (29 g.), added to a solution of the ketone hydrochloride (61.2 g.) in hot alcohol, produced immediate crystallisation. Acetic acid (29 g.) dissolved in alcohol was added and after 15 minutes the crystals were collected and washed with alcohol. The product was refluxed with alcohol to remove traces of impurities, and the yellow crystalline phenylhydrazone so obtained (65 g.) was pure; m. p. 180° (Found : N, 10.0. $C_{24}H_{33}ON_3$, HCl requires N, 10·1%). Its isomerisation was accomplished by heating 40 g. for 1 hour on the steam-bath with acetic acid (120 g.) and water (600 ml.). The procedure described for the corresponding β -diethylaminoethyl compound was then followed, the product separating from the light petroleum in pale yellow crystals (20 g.), m. p. 63°. 1-Phenyl-5-panisyl-3- β -di-n-propylaminoethylpyrazoline was obtained in colourless needles by distillation in a vacuum, followed by crystallisation from light petroleum (Found: C, 75.7; H, 9.0; N, 11.4. C₂₄H₃₃ON₃ requires C, 75.9; H, 8.9; N, 11.1%).

1-Di-n-butylamino-5-p-anisyl- Δ^4 -penten-3-one Hydrochloride.—A mixture of di-n-butylamine hydrochloride (36.8 g.), anisylideneacetone (39.0 g.), paraformaldehyde (11.0 g.), and 90% alcohol (70 ml.) was heated on the steam-bath for 75 minutes. A further quantity of paraformaldehyde (5 g.) was added, and heating continued for an hour. The solution was evaporated to small bulk and the crystals which formed were separated from a viscous syrup and washed with acetone-ether. Yield, 12.5 g., m. p. 65—68°. Recrystallisation from acetone gave 6.7 g., m. p. 66—68° (Found : C, 63.9; H, 9.7. C₂₀H₃₁O₂N,HCl requires C, 67.9; H, 9.05%). The phenylhydrazone formed yellow crystals, m. p. 167—168° (Found : C, 70.2; H, 9.0. C₂₈H₃₇ON₃,HCl requires C, 70.3; H, 8.6%).

1-Phenyl-5-p-anisyl-3- β -di-n-butylaminoethylpyrazoline.—The above phenylhydrazone (5 g.) was heated on the steam-bath for 90 minutes with glacial acetic acid (12 ml.) and water

(50 ml.). The filtered solution was basified and extracted with ether. The crude base was a thick brown oil (4.2 g.), b. p. $265-267^{\circ}/1$ mm. The distillate began to crystallise after about 6 months and then formed waxy crystals, m. p. 26-27°, very readily soluble in organic solvents, but insoluble in water (Found: N, 10.6. C26H37ON3 requires N, 10.3%). The tartrate, lactate, sulphate, and hydrochloride were syrups which did not crystallise.

Phenylhydrazone of 1-Piperidino-5-p-anisyl- Δ^4 -penten-3-one Hydrochloride.—To the ketonebase hydrochloride (14.75 g.) (Mannich and Schütz, loc. cit.), dissolved in warm alcohol (300 ml.), were added phenylhydrazine (5.4 g.) and glacial acetic acid (5.4 g.). The solid obtained on cooling and standing overnight crystallised from alcohol in pale yellow needles, m. p. 188° (Found : N, 10.5. C₂₃H₂₉ON₃,HCl requires N, 10.6%).

1-Phenyl-5-p-anisyl-3-β-piperidinoethylpyrazoline.--The above phenylhydrazone (10 g.) was heated on the steam-bath for 25 minutes with glacial acetic acid (50 ml.). The solution was cooled, basified, and extracted with ether. After drying over sodium sulphate, removal of the ether gave an oil (8 g.), which separated from light petroleum in pale yellow crystals (4 g.), m. p. 88° (Found : C, 75.9; H, 8.2; N, 11.8. C₂₃H₂₉ON₃ requires C, 76.0; H, 8.0; N, 11.6%).

The isomerisation was also accomplished by heating the phenylhydrazone hydrochloride with acetic acid diluted with water or absolute alcohol; the hydrochloride of the base could then be isolated directly (see also below) or as the base by the procedure described above.

Hydrochloride. The phenylhydrazone hydrochloride (m. p. 188°; 12 g.), heated on the steam-bath for $\frac{1}{2}$ hour with 110 ml. of N-hydrochloric acid, gradually changed into the colourless pyrazoline hydrochloride. On cooling, a crystalline mass was obtained (12 g.). Recrystallised from boiling water, it formed colourless needles, m. p. 215° (Found: Cl, 8.9. $C_{23}H_{29}ON_3$, HCl requires Cl, 8.9%).

Sulphate. 2.3 G. of the crystalline base (m. p. 88°) were treated with 5.7 ml. of N/10sulphuric acid and dissolved in alcohol. On removal of the solvent a glassy solid remained. To this, benzene was added, and gradually distilled off until crystals began to separate; distillation was then stopped, and the solution allowed to cool. Crystals of the acid sulphate were collected and recrystallised from acetone; m. p. 172° (decomp.) (Found: S, 70. $C_{23}H_{29}ON_3, H_2SO_4$ requires S, 6.9%).

Tartrate. A neutral tartrate was obtained by dissolving the base (1 g.) in methyl alcohol and adding tartaric acid (0.2 g.). Evaporation of the solvent left a syrup, a solution of which in acetone deposited crystals on concentration; m. p. 115° (decomp.) (Found: C, 68.6; H, 7.5. $C_{23}H_{29}ON_3, \frac{1}{2}C_4H_6O_6$ requires C, 68.5; H, 7.3%).

The p-tolylhydrazone of 1-piperidino-5-p-anisyl- Δ^4 -penten-3-one hydrochloride, obtained analogously to the phenylhydrazor: described above, formed yellow needles, m. p. 176-177°, from methyl alcohol (Found : C, 70·1; H, 8·0. $C_{24}H_{31}ON_3$, HCl requires C, 69·65; H, 7·7%). Isomerisation with dilute acetic or hydrochloric acid gave white needles (from boiling water), m. p. 204°, of 1-p-tolyl-5-p-anisyl-3-β-piperidinoethylpyrazoline hydrochloride (Found : Cl, 8.5. $C_{24}H_{22}ON_3$, HCl requires Cl, 8.6%).

1-Dibenzylamino-5-p-anisyl- Δ^4 -penten-3-one Hydrochloride.—Dibenzylamine hydrochloride (23.3 g.), anisylideneacetone (18 g.), paraformaldehyde (5 g.) and alcohol (54 ml.) were heated on the steam-bath for an hour. The crystals (m. p. $160-220^{\circ}$) which separated on cooling were collected and washed with alcohol and ether; the filtrate was evaporated and refiltered. The second crop (38.7 g.; m. p. 170-220°) was crystallised twice from alcohol and then gave colourless leaflets, m. p. 225-230° (decomp.) after sintering at 160° (Found: N, 4.25. $C_{26}H_{23}O_2N$,HCl requires N, 3.3%. The nitrogen content is equivalent to admixture with the amino-ketone hydrochloride of 30% of unchanged dibenzylamine hydrochloride).

Phenylhydrazone. A solution of the amino-ketone hydrochloride (10 g.), phenylhydrazine (3 g.), and glacial acetic acid (3 ml.) in warm alcohol (70 ml.) was kept; crystallisation began in a few minutes. After standing overnight, the yellow crystals were collected and washed with alcohol; yield, 7.5 g.; m. p. 235-240° (softening at about 190°) (Found: N. 8.4. $C_{32}H_{33}ON_3$, HCl requires N, 8.2%).

1-Phenyl-5-p-anisyl-3-β-dibenzylaminoethylpyrazoline (?).—A mixture of the above phenylhydrazone (32.9 g.), glacial acetic acid (70 ml.), and water (280 ml.) was heated on the steambath for 2 hours. The hydrochloride was converted into a thick brown oil. This was partly soluble in ether, and the ethereal extract was filtered, leaving some unchanged phenylhydrazone (identity confirmed by m. p.). The filtrate was evaporated, and the residue digested with concentrated hydrochloric acid; it then became almost completely ether-insoluble. It was washed with ether and warmed with 5N-sodium hydroxide, becoming almost completely ethersoluble again. The ethereal extract was treated with charcoal and evaporated, leaving a

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thick brownish-red syrup, which slowly set to a vitreous solid. It distilled apparently unchanged, b. p. 300—310°/1 mm., giving a thick, light brown oil, which did not crystallise. It was insoluble in acetic, sulphuric or tartaric acid.

Action of Hydrazine on 1-Piperidino-5-p-anisyl- Δ^4 -penten-3-one Hydrochloride.—Hydrazine sulphate (13 g.) and the ketone hydrochloride (30 g.) in alcohol (100 ml.) were heated on the steam-bath, and sodium bicarbonate (25.2 g.) added; after 3—4 hours, the solution was cooled, made alkaline with sodium hydroxide, and extracted with ether. After drying, removal of the ether gave a syrup, which deposited a resinous solid. (Use of hydrazine hydrate or acetate in place of the sulphate gave a similar product.) The oil decanted from the resin was dissolved in alcohol and neutralised with succinic acid. On concentration, crystals separated, which were recrystallised from acetone; m. p. 137°. The salt had an acid reaction and was soluble in water (Found : N, 7.1; succinic acid, by titration, 30.3. The true hydrazone succinate, $C_{17}H_{25}ON_3, C_4H_6O_4$ requires N, 7.9; succinic acid, 22.6%. The succinate isolated is thus obviously not that of the required hydrazone; it may be that of the ketazine, $C_{34}H_{46}O_4N_4, 2C_4H_6O_4$, which requires N, 7.2; succinic acid, 30.3%).

1-Piperidino-5-p-anisyl- Δ^4 -penten-3-one Oxime Hydrochloride.—The keto-base hydrochloride (5 g.), hydroxylamine hydrochloride (1·1 g.), and sodium bicarbonate (1·6 g.) were dissolved in aqueous alcohol and heated under reflux on the steam-bath for 2 hours. The solution was then neutralised with hydrochloric acid and concentrated. On cooling, the hydrochloride (2·5 g.), m. p. 208°, was obtained (Found : Cl, 10·9. $C_{17}H_{24}O_2N_2$,HCl requires N, 10·9%). The base was obtained directly from another preparation. After 2 hours' heating, the solution was evaporated to dryness in a vacuum, and the residue extracted with hot absolute alcohol; on cooling, crystals (3 g.), m. p. 166°, separated (Found : C, 70·7; H, 8·7; N, 9·9. $C_{17}H_{24}O_2N_2$ requires C, 70·8; H, 8·3; N, 9·7%). The hydrochloride and the sulphate were sparingly soluble, but a neutral solution of a lactate was obtained by neutralisation with lactic acid.

Hydrolysis. The oxime (0.5 g.) was heated on the steam-bath with concentrated hydrochloric acid, the solution evaporated to dryness, and the residue crystallised from alcohol and then from acetone. Colourless crystals, m. p. 184°, identical with 1-piperidino-5-*p*-anisyl- Δ^4 penten-3-one hydrochloride were obtained.

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HERIOT WATT COLLEGE, EDINBURGH.

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