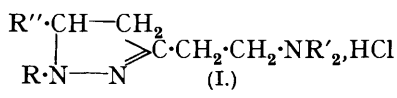
293. *Pyrazoline Local Anæsthetics. Part II. Derivatives of Alkylated 3 : 4-Dihydroxybenzylideneacetones.*

By Hugh B. Nisbet.

The unsaturated β-amino-ketones derived from alkylated derivatives of 3 : 4-dihydroxybenzylideneacetones by condensation with formaldehyde and secondary base hydrochlorides have been converted into phenylhydrazones or *p*-tolylhydrazones and isomerised to give pyrazolines of type (I), in which the 5-phenyl radical carries alkoxyl groups in positions 3′ and 4′. Pharmacological examination indicates that the effect of the introduction of such alkoxyl groups in this phenyl radical is to increase the local anæsthetic activity and at the same time to reduce the toxicity of such pyrazolines. Partial resolution of the *tartrate* of 1-phenyl-5-(3′-methoxy-4′-ethoxyphenyl)-3-β-dimethylaminoethylpyrazoline has been accomplished, but the anæsthetic activities of the salts of the active and the racemic bases do not differ significantly.

The introduction of alkoxyl groups often has a very marked effect on the pharmacological properties of drugs of various kinds, including local anæsthetics. For instance, Bovet (*Arch. internat. Pharm. Therap.*, 1931, **41**, 103) has shown that the presence of an alkoxyl group at position 6 in 8-(γ-diethylamino-ββ-dimethylpropylamino)-6-ethoxyquinoline is of the greatest importance for the local anæsthetic activity, and Rohman and Scheurle (*Arch. Pharm.*, 1936, **274**, 110), in a study of the relationship between the chemical constitution and pharmacological action of alkylamine esters of *p*-alkoxybenzoic acids, found that increase in the size of the alkoxyl group was accompanied by an increase in the activity, straight chains being more effective than branched.

In Part I (this vol., p. 1237) it was shown that pyrazolines of type (I; R, R″ = phenyl or substituted phenyl; NR'_2 = dialkylamino- or piperidino-) possess local anæsthetic activity, and the effect of varying the groups R and NR'_2 was studied. In order to extend this study to the effect of introducing alkoxyl groups in the phenyl group R″, numerous derivatives of this type have been synthesised. From unsaturated ketones such as veratrylidene-, piperonylidene-, vanillylidene-, *ethylvanillylidene*-, and *ethyl*iso*vanillylidene*-acetone, by condensation with formaldehyde and the hydrochlorides of dimethylamine, diethylamine, or piperidine, a series of unsaturated amino-ketones was obtained. These were converted into their phenyl- or *p*-tolyl-hydrazones, which were isomerised to the corresponding pyrazolines.



(I.)

Pharmacological examination (cf. Sinha, Thesis, Edinburgh, 1935; *J. Pharm. Exp. Therap.*, in the press) indicates that the introduction of alkoxyl groups into the 5-phenyl nucleus increases the local anæsthetic activity and, at the same time, decreases the toxicity. The presence of a hydroxyl group in this nucleus greatly decreases the activity, but the interchange of methoxy- and ethoxy-groups at positions 3′ and 4′ has little effect on these properties.

For the pharmacological tests the hydrochlorides were used in most cases. From 1-*phenyl*-5-(3′-*methoxy*-4′-*ethoxyphenyl*)-3-β-*dimethylaminoethylpyrazoline hydrochloride* a *tartrate* was prepared and, by repeated crystallisation, the least soluble portion was finally obtained with a constant rotation $[\alpha]_D^{20°}$ — 36·7°. This resolution, the only one yet attempted, had apparently but little effect on the anæsthetic activity. There is not sufficient evidence available to indicate in general the effect of the use of tartrates instead of hydrochlorides of this pyrazoline type of local anæsthetic.

Among the more active anæsthetics now described is 1-*phenyl*-5-(4′-*methoxy*-3′-*ethoxy*-

phenyl)-3-β-*piperidinoethylpyrazoline hydrochloride*, of which the pharmacology has been studied by Sinha (*ibid.*, 1936, **57**, 199). Although this compound is only slightly more toxic than cocaine, it is considerably more active than the latter for the production of local anæsthesia as tested by the rabbit's cornea and human wheal methods. It was found, however, to be of little use for the production of nerve block, but may be of value for clinical application to mucosæ or for infiltration anæsthesia.

Experimental.

Ethylvanillylideneacetone and *ethyliso*vanillylideneacetone were prepared from ethyl-vanillin and -*iso*vanillin and acetone by suitable modification of the process for benzylideneacetone (" Organic Syntheses," Vol. III, 17). They crystallised from 95% alcohol as yellow needles, m. p. 105° (Found : C, 70·4; H, 7·3. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%) and m. p. 92—93° (Found : C, 70·4; H, 7·3%), respectively.

Vanillylideneacetone. Attempts to prepare this by Francesconi and Cusamo's method (*Gazzetta*, 1908, **38**, ii, 75; see Beilstein, **8**, 291) failed to give any of the desired product. [Hydroxyaldehydes frequently fail to condense; *e.g.*, β-resorcylaldehyde with 1-hydrindone (Perkin, Robinson, and Turner, J., 1908, **33**, 1085); hydroxyaldehydes with styryl methyl ketones (Buck and Heilbron, J., 1922, **121**, 1095).] Condensation was effected, however, by a modification of Harries's method (*Ber.*, 1891, **24**, 3180) for the preparation of salicylideneacetone. Vanillin (124 g.), dissolved in acetone (500 ml.), was treated with 170 ml. of 50% sodium hydroxide; the resulting solid mass was dissolved by addition of water (300 ml.), the solution heated under reflux on the steam-bath for about 5 mins., and set aside at room temperature for 48 hours. A deep red solution was obtained on which floated orange-red crystals. The solution was made just acid with acetic acid, and most of the acetone removed on the steam-bath. On cooling, an oil separated, which crystallised on standing; recrystallisation, first from acetone and then from light petroleum, afforded pale yellow crystals, m. p. 129°; yield, 80 g.

Preparation of Pyrazolines.—The above and similar alkylated derivatives of 3 : 4-dihydroxybenzylideneacetones were heated in alcoholic solution with the hydrochlorides of secondary bases and paraformaldehyde until homogeneous. By cooling and scratching or digesting with acetone or ether, the hydrochlorides of the desired β-amino-ketones were isolated. The purified products were converted into phenylhydrazones or *p*-tolylhydrazones, and these were isomerised to the corresponding pyrazolines by heating for a short time with aqueous or alcoholic acetic acid (approximately 20%) or N-hydrochloric acid. In some cases, the pyrazoline hydrochlorides separated from the reaction mixtures or were obtained on evaporation in a vacuum; in others, the product of the isomerisation was isolated as the base. One of the pyrazolines was obtained from the β-amino-ketone without isolation of the intermediate hydrazone.

1-*Phenyl*-5-(3′ : 4′-*dimethoxyphenyl*)-3-β-*diethylaminoethylpyrazoline*.—1-Diethylamino-5-(3′ : 4′-dimethoxyphenyl)-Δ^4-penten-3-one hydrochloride, crystallised twice from alcohol with ice-cooling, formed colourless needles, m. p. 141—142° (Mannich and Schütz, *Arch. Pharm.*, 1927, **265**, 684, give m. p. 134°) (Found : C, 61·8; H, 8·0; N, 4·3. Calc. for $C_{17}H_{25}O_3N$,HCl : C, 62·3; H, 7·9; N, 4·3%); *phenylhydrazone*, fine yellow needles from alcohol, m. p. 175° (Found : C, 65·8; H, 7·9; N, 10·3. $C_{23}H_{31}O_2N_3$,HCl requires C, 66·1; H, 7·7; N, 10·1%). The *pyrazoline* was obtained by heating the phenylhydrazone hydrochloride (55 g.) on the steam-bath for 40 mins. with 20% acetic acid (700 ml.). The green solution was basified, and the yellow base extracted by ether; yield, 47·8 g., 95%. Crystallisation from light petroleum (b. p. 60—80°) gave needles, m. p. 93—96° (Found : C, 72·0; H, 8·8; N, 11·0. $C_{23}H_{31}O_2N_3$ requires C, 72·4; H, 8·1; N, 11·0%). The *acid succinate* crystallised when a neutral solution of the base in succinic acid was kept for several weeks; crystallised from aqueous acetone, it had m. p. 94—95° (Found : N, 8·4. $C_{23}H_{31}O_2N_3$,$C_4H_6O_4$ requires N, 8·4%). The hydrochloride, from acetone, had m. p. 139—140°, but the sulphate could not be crystallised.

1-*Phenyl*-5-(3′ : 4′-*dimethoxyphenyl*)-3-β-*piperidinoethylpyrazoline*.—The phenylhydrazone of 1-piperidino-5-(3′ : 4′-dimethoxyphenyl)-Δ^4-penten-3-one hydrochloride was obtained as yellow needles from alcohol, m. p. 201—202° (decomp.) (Mannich and Schütz, *loc. cit.*, give m. p. 195°) (Found : C, 67·2; H, 7·9; N, 9·85. Calc. for $C_{24}H_{31}O_2N_3$,HCl : C, 67·1; H, 7·5; N, 9·8%). This hydrochloride (39·1 g.) was heated on the steam-bath for 30 minutes with 500 ml. of 20% acetic acid, and the dark green solution was evaporated. The syrupy residue partly crystallised on scratching. Digested with acetone and filtered, this yielded the hydrochloride (21·6 g.),

m. p. 196—200°. The *base* was liberated by adding sodium hydroxide to the crude hydrochloride dissolved in warm water. It formed a thick gum (16·8 g.), which set to a solid mass after several days. Repeated crystallisation of the base from light petroleum (b. p. 40—60°), of the hydrochloride from water, and of the regenerated base again from light petroleum (b. p. 60—80°) did not afford a product of sharper m. p. than 79—84° (Found: C, 73·2; H, 8·3; N, 10·8. $C_{24}H_{31}O_2N_3$ requires C, 73·3; H, 7·9; N, 10·7%). The *acid sulphate* had m. p. 157—160° (Found: C, 58·3; H, 7·0; S, 6·6. $C_{24}H_{31}O_2N_3,H_2SO_4$ requires C, 58·7; H, 6·7; S, 6·5%).

1-*Phenyl*-5-(3′ : 4′-*methylenedioxyphenyl*)-3-β-*dimethylaminoethylpyrazoline Hydrochloride.*—1-*Dimethylamino*-5-(3′ : 4′-*methylenedioxyphenyl*)-Δ^4-*penten*-3-*one hydrochloride*, prepared from piperonylideneacetone, dimethylamine, and paraformaldehyde, crystallised from alcohol in pale rosettes of squat, yellow needles, m. p. 163—164° (Found: C, 59·1; H, 6·4. $C_{14}H_{17}O_3N,HCl$ requires C, 59·3; H, 6·3%). The phenylhydrazone (fine yellow needles, m. p. 160—161°, from methyl alcohol) was isomerised with dilute acetic acid. The pyrazoline *hydrochloride*, crystallised twice from a small quantity of alcohol (ice-cooling), formed compact clusters of needles, m. p. 194° (Found: Cl, 9·52. $C_{20}H_{23}O_2N_3,HCl$ requires Cl, 9·50%).

1-p-*Tolyl*-5-(3′ : 4′-*methylenedioxyphenyl*)-3-β-*dimethylaminoethylpyrazoline Hydrochloride.*—To 1-dimethylamino-5-(3′ : 4′-methylenedioxyphenyl)-Δ^4-penten-3-one hydrochloride (7·1 g.), dissolved in water (50 ml.) and acetic acid (10 ml.), *p*-tolylhydrazine hydrochloride (4 g.) was added, and the mixture boiled under reflux for 20 mins. The filtered solution was evaporated on the water-bath and kept for several days in a vacuum over sodium hydroxide and calcium chloride. The solid so obtained was crystallised from alcohol, forming yellowish-white needles, m. p. 182—184°; yield, 3·4 g. (Found: Cl, 9·14. $C_{21}H_{25}O_2N_3,HCl$ requires Cl, 9·16%).

1-*Phenyl*-5-(3′ : 4′-*methylenedioxyphenyl*)-3-β-*piperidinoethylpyrazoline hydrochloride* was obtained from the phenylhydrazone of 1-piperidino-5-(3′ : 4′-methylenedioxyphenyl)-Δ^4-penten-3-one hydrochloride (cf. Mannich and Schütz, *loc. cit.*), and crystallised from water; m. p. 196—197° (Found: Cl, 8·5. $C_{23}H_{27}O_2N_3,HCl$ requires Cl, 8·6%).

1-*Phenyl*-5-(4′-*methoxy*-3′-*ethoxyphenyl*)-3-β-*dimethylaminoethylpyrazoline Hydrochloride.*—1-*Dimethyamino*-5-(4′-*methoxy*-3′-*ethoxyphenyl*)-Δ^4-*penten*-3-*one hydrochloride* was obtained from 4-methoxy-3-ethoxybenzylideneacetone, dimethylamine hydrochloride, and paraformaldehyde as white needles, m. p. 161—162° (Found: N, 4·6. $C_{16}H_{23}O_3N,HCl$ requires N, 4·5%), from alcohol; *phenylhydrazone*, m. p. 178° (Found: C, 65·8; H, 7·45. $C_{22}H_{29}O_2N_3,HCl$ requires C, 65·4; H, 7·4%); p-*tolylhydrazone*, m. p. 173° (Found: C, 62·0; H, 7·7. $C_{23}H_{31}O_2N_3,HCl,1\frac{1}{2}H_2O$ requires C, 62·1; H, 7·9%). The phenylhydrazone was isomerised with dilute acetic acid, and the pyrazoline hydrochloride formed white needles from water, m. p. 72—78° (Found: C, 61·8; H, 7·6; Cl, 8·5. $C_{22}H_{29}O_2N_3,HCl,H_2O$ requires C, 62·6; H, 7·6; Cl, 8·4%). 1-p-*Tolyl*-5-(4′-*methoxy*-3′-*ethoxyphenyl*)-3-β-*dimethylaminoethylpyrazoline hydrochloride* was similarly obtained from the *p*-tolylhydrazone. It separates from water and then alcohol as a white solid of indefinite m. p., which can be raised to 152° by drying (Found: Cl, 8·1. $C_{23}H_{31}O_2N_3,HCl,H_2O$ requires Cl, 8·15%).

1-*Phenyl*-5-(4′-*methoxy*-3′-*ethoxyphenyl*)-3-β-*diethylaminoethylpyrazoline.*—1-*Diethylamino*-5-(4′-*methoxy*-3′-*ethoxyphenyl*)-Δ^4-*penten*-3-*one hydrochloride* was obtained by heating 4-methoxy-3-ethoxybenzylideneacetone (83 g.) with diethylamine hydrochloride (42 g.) and paraformaldehyde (12 g.) in 90% alcohol (90 ml.) on the steam-bath for 30 mins. After standing in the ice-chest for 3 days, the mixture was digested with dry ether and filtered. From the filtrate, by precipitation with ether, a pale yellow solid, soluble in acetone, was obtained (80 g.; m. p. 74—80°). Reprecipitation from acetone solution with ether gave a solid (74 g.; m. p. 105—111°), which crystallised from acetone–ether, m. p. 132—134° (Found: C, 62·9; H, 8·1; N, 4·3. $C_{18}H_{27}O_3N,HCl$ requires C, 63·3; H, 8·2; N, 4·1%). The *phenylhydrazone* (m. p. 173°. Found: C, 66·5; H, 8·3. $C_{24}H_{33}O_2N_3,HCl$ requires C, 66·7; H, 7·9%) (25·8 g.) was isomerised by heating on the steam-bath for 45 mins. with a solution of acetic acid (60 g.) in water (250 ml.). The solution was basified, and the *pyrazoline* extracted with ether. After two crystallisations from light petroleum, it had m. p. 50—51° (Found: C, 73·0; H, 8·4. $C_{24}H_{33}O_2N_3$ requires C, 72·9; H, 8·3%).

1-*Phenyl*-5-(4′-*methoxy*-3′-*ethoxyphenyl*)-3-β-*piperidinoethylpyrazoline Hydrochloride.*—1-*Piperidino*-5-(4′-*methoxy*-3′-*ethoxyphenyl*)-Δ^4-*penten*-3-*one hydrochloride* was prepared from 4-methoxy-3-ethoxybenzylideneacetone, piperidine hydrochloride, and paraformaldehyde, and crystallised from alcohol, m. p. 162° (Found: N, 4·1. $C_{19}H_{27}O_3N,HCl$ requires N, 4·0%). The *phenylhydrazone*, yellow needles, m. p. 184° (Found: C, 68·05; H, 7·6. $C_{25}H_{33}O_2N_3,HCl$ requires C, 67·7; H, 7·7%), was readily isomerised on boiling with N-hydrochloric acid. The *pyrazoline hydrochloride* was obtained in almost theoretical yield, and crystallised from water in

white needles, m. p. 192° (Found : Cl, 7·9. $C_{25}H_{33}O_2N_3$,HCl requires Cl, 8·0%). Isomerisation of the p-*tolylhydrazone*, yellow needles, m. p. 183° (Found : C, 67·6; H, 7·85. $C_{26}H_{35}O_2N_3$,HCl requires C, 68·2; H, 7·9%), by boiling with 20% acetic acid for 10 mins., gave 1-p-*tolyl*-5-(4′-*methoxy*-3′-*ethoxyphenyl*)-3-β-*piperidinoethylpyrazoline hydrochloride*, which crystallised from alcohol and then from water in white, microcrystalline needles, m. p. 178° (Found : C, 66·0; H, 8·0; Cl, 7·5; N, 9·2. $C_{26}H_{35}O_2N_3$,HCl,H_2O requires C, 65·6; H, 8·0; Cl, 7·5; N, 8·8%).

1-*Phenyl*-5-(3′-*methoxy*-4′-*ethoxyphenyl*)-3-β-*dimethylaminoethylpyrazoline Hydrochloride*.—1-*Dimethylamino*-5-(3′-*methoxy*-4′-*ethoxyphenyl*)-Δ^4-*penten*-3-*one hydrochloride*, obtained from 3-methoxy-4-ethoxybenzylideneacetone, dimethylamine hydrochloride and paraformaldehyde, had m. p. 165° (Found : N, 4·4. $C_{16}H_{23}O_3N$,HCl requires N, 4·5%). The *phenylhydrazone*, yellow needles, m. p. 177° (Found : C, 65·95; H, 7·4. $C_{22}H_{29}O_2N_3$,HCl requires C, 65·4; H, 7·4%), was isomerised with either 20% acetic acid or N-hydrochloric acid, and the *pyrazoline hydrochloride* was crystallised from alcohol and then from water; m. p. 123° after softening at 114° (Found : C, 62·05, 61·9; H, 7·7, 7·6; Cl, 8·4. $C_{22}H_{29}O_2N_3$,HCl,H_2O requires C, 62·6; H, 7·6; Cl, 8·4%). The base (14·48 g.) obtained from this hydrochloride was dissolved in a very small quantity of alcohol and treated with a solution of tartaric acid (6 g.) in alcohol; the white *acid tartrate* (m. p. 134°) soon separated (Found : $C_4H_6O_6$, 29·0. $C_{22}H_{29}O_2N_3$,$C_4H_6O_6$ requires $C_4H_6O_6$, 29·0%). By repeated crystallisation of the least soluble portion of this tartrate, a fraction of constant rotation, $[\alpha]_D^{20°}$ — 36·7°, was finally obtained; m. p. 134° (Found : C, 60·1; H, 6·3. $C_{22}H_{29}O_2N_3$,$C_4H_6O_6$ requires C, 60·3; H, 6·8%). From the first mother-liquors a small fraction with $[\alpha]_D^{22°}$ + 4·23° was isolated, but in insufficient quantity to be worked up to constant rotation.

The p-*tolylhydrazone* of the above amino-ketone hydrochloride, yellow needles, m. p. 174° (Found : C, 66·0; H, 7·2; N, 10·2. $C_{23}H_{31}O_2N_3$,HCl requires C, 66·1; H, 7·7; N, 10·1%), was isomerised with 20% acetic acid to 1-p-*tolyl*-5-(3′-*methoxy*-4′-*ethoxyphenyl*)-3-β-*dimethylaminoethylpyrazoline hydrochloride*, which was crystallised first from water and then from alcohol, m. p. 181° (Found : C, 61·9; H, 7·7; Cl, 8·1. $C_{23}H_{31}O_2N_3$,HCl,$1\frac{1}{2}H_2O$ requires C, 62·1; H, 7·9; Cl, 8·0%).

1-*Phenyl*-5-(3′-*methoxy*-4′-*ethoxyphenyl*)-3-β-*piperidinoethylpyrazoline Hydrochloride*.—1-*Piperidino*-5-(3′-*methoxy*-4′-*ethoxyphenyl*)-Δ^4-*penten*-3-*one hydrochloride*, prepared from 3-methoxy-4-ethoxybenzylideneacetone, piperidine hydrochloride, and paraformaldehyde, formed white needles from alcohol, m. p. 167° (Found : Cl, 10·1. $C_{19}H_{27}O_3N$,HCl requires Cl, 10·0%). The *phenylhydrazone*, small yellow needles, m. p. 167° (Found : C, 67·5; H, 7·6. $C_{25}H_{33}O_2N_3$,HCl requires C, 67·7; H, 7·7%), was isomerised by boiling with alcoholic acetic acid, and the *pyrazoline hydrochloride* formed white needles from alcohol, m. p. 172—173° (Found : Cl, 8·2. $C_{25}H_{33}O_2N_3$,HCl requires Cl, 8·0%). The p-*tolylhydrazone*, m. p. 176—178° (Found : C, 67·95; H, 7·85. $C_{26}H_{35}O_2N_3$,HCl requires C, 68·2; H, 7·9%), isomerised with aqueous acetic acid, gave 1-p-*tolyl*-5-(3′-*methoxy*-4′-*ethoxyphenyl*)-3-β-*piperidinoethylpyrazoline hydrochloride*; white needles from water containing a little acetic acid, m. p. 183° after sintering at 100° (Found : Cl, 7·7. $C_{26}H_{35}O_2N_3$,HCl requires Cl, 7·8%).

1-*Phenyl*-5-*vanillyl*-3-β-*piperidinoethylpyrazoline*.—1-*Piperidino*-5-*vanillyl*-Δ^4-*penten*-3-*one hydrochloride*, from vanillylideneacetone, piperidine hydrochloride, and paraformaldehyde, separated as white needles from alcohol, m. p. 180° (Found : Cl, 11·2. $C_{17}H_{23}O_3N$,HCl requires Cl, 10·9%). The *phenylhydrazone*, yellow needles, m. p. 196° (Found : N, 10·0. $C_{23}H_{29}O_2N_3$,HCl requires N, 10·1%), was isomerised with aqueous acetic acid, and the free *pyrazoline* was isolated as colourless crystals (from benzene), m. p. 174° (Found : C, 72·4; H, 7·8; N, 11·1. $C_{23}H_{29}O_2N_3$ requires C, 72·8; H, 7·65; N, 11·1%).

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HERIOT-WATT COLLEGE, EDINBURGH. [*Received, July 27th*, 1938.]