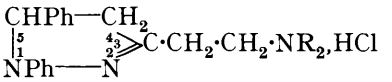
294. *Pyrazoline Local Anæsthetics. Part III. Derivatives of o-Alkoxybenzylideneacetones.*

By G. A. Levvy and Hugh B. Nisbet.

Various alkylated salicylideneacetones have been converted by the Mannich reaction into unsaturated β-amino-ketones of type (II). The phenylhydrazones of these have been isomerised to pyrazolines (III), in which the 5-phenyl radical carries an *o*-methoxy-, -ethoxy-, -*n*-propoxy-, or -*n*-butoxy-group.

The pharmacological examination of these pyrazolines indicated that, except the *o*-*n*-propoxy-compound, they are more potent than cocaine in producing local anæsthesia of the rabbit's cornea and in the human wheal test. None was at all irritant, and the three active members were less toxic than cocaine when tested by intraperitoneal injection in mice. The *o*-*n*-butoxy-compound was found to be the most effective local anæsthetic of this series.

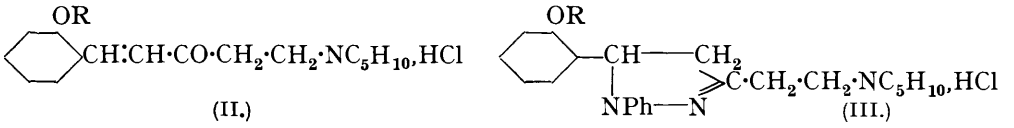
It was shown in Part II (preceding paper) that introduction of alkoxyl groups in positions 3′ and 4′ in the 5-phenyl radical in pyrazolines of type (I) increased the activity of such



(I.)

compounds as local anæsthetics, and decreased their toxicity. In order to study the effect of alkoxyl groups in the 2′-position in the 5-phenyl radical upon local anæsthetic activity and toxicity, a number of such compounds have now been synthesised.

By alkylating salicylideneacetone and condensing the resulting *o*-alkoxybenzylideneacetones with formaldehyde and piperidine hydrochloride, a series of compounds of type (II) have been prepared. Their phenylhydrazones were obtained by the method of Auwers



(II.) (III.)

(R = Me, Et, *n*-Pr, *n*-Bu.)

and Voss (*Ber.*, 1909, **42**, 4411), but some of them did not separate readily from the reaction mixtures. All four, however, proved to be isomorphous, each crystallising at once when its solution was seeded with any of the others.

On repeated crystallisation of the phenylhydrazone of the *o*-ethoxy-derivative (II, R = Et), its m. p. fell and became less sharp, suggesting that some isomerisation to the corresponding pyrazoline (III, R = Et) occurred in hot alcohol. The readiness with which rearrangement of the phenylhydrazones of α-unsaturated ketones may take place is well known. As expected, the phenylhydrazone in question answered Knorr's test for pyrazolines. With the phenylhydrazone of the lower homologue (II, R = Me), Knorr's test was inconclusive. The *phenylhydrazones* of (II, R = *n*-Pr) and (II, R = *n*-Bu) did not respond to the test. No colour change was observed on spreading any one of the four phenylhydrazones on filter paper and exposing it to bromine vapour (cf. Raiford and Peterson, *J. Org. Chem.*, 1937, **1**, 544), and this test has been found, in general, more valuable than Knorr's reaction as a method of distinguishing phenylhydrazones from their isomeric pyrazolines.

Isomerisation of the phenylhydrazones to the corresponding pyrazolines proceeded smoothly on warming them for a short time with N-hydrochloric acid (cf. Part I, this vol., p. 1237). On exposing any one of these to bromine vapour, an immediate colour change to blue-violet was observed.

The pharmacological examination of the pyrazolines (III) (Levvy and Nisbet, *J. Pharm. Exp. Therap.*, in the press) indicated that, with one exception (R = *n*-Pr), they were all more potent than cocaine in producing local anæsthesia of the rabbit's cornea and were

very powerful when injected intracutaneously. None of the pyrazolines was at all irritant. The toxicities of the three active members, determined by intraperitoneal injection in mice, were less than that of cocaine. From the results, it appears that the *n*-butoxy-compound (III, R = *n*-Bu) is the most effective member of this series as a local anæsthetic.

Attempts have been made to replace the piperidino-group in 1-piperidino-5-(2′-*n*-butoxyphenyl)-Δ^4-penten-3-one hydrochloride (II, R = *n*-Bu) by dimethylamino-, diethylamino-, di-*n*-propylamino-, and di-*n*-butylamino-groups, but only the second of these compounds has been isolated, and attempts to convert it into the pyrazoline failed.

Experimental.

2-Ethoxybenzylideneacetone.—Salicylideneacetone (30 g.) and ethyl iodide (32 g.) in absolute alcohol (100 ml.) were treated with potassium hydroxide (14 g., dissolved in the minimum of water) and heated under reflux on the water-bath for 1½ hours. The mixture was poured into water (3 l.), the oil which separated was extracted with ether, and the extract washed with dilute sodium hydroxide and water, and dried over potassium carbonate. The red oil obtained by removal of the ether gave a yellow solid on cooling. Distillation at 1 mm. gave an almost colourless oil (b. p. 143—145°) which solidified on cooling. It was soluble in the usual solvents, but not readily crystallisable (Found: C, 75·5; H, 7·3. $C_{12}H_{14}O_2$ requires C, 75·8; H, 7·4%).

2-n-*Propoxybenzylideneacetone.*—This was prepared analogously by alkylation with *n*-propyl iodide; it distilled over a wide range, approx. 155—165°/1 mm., and showed but little tendency to solidify in the cold; yield 35% (Found: C, 76·6; H, 7·5. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8%).

2-n-*Butoxybenzylideneacetone.*—Salicylideneacetone (178 g.) and *n*-butyl *p*-toluenesulphonate (228 g.) were dissolved in 90% alcohol (500 ml.), and potassium hydroxide (70 g., dissolved in the minimum of water) added. After being heated under reflux on the water-bath for 1½ hours, the reaction mixture was poured into water (5 l.), and the oil which separated was extracted with ether. The extract was washed with 2% sodium hydroxide solution and water, and dried over potassium carbonate. Removal of the ether gave an oil, which was best distilled in 25-ml. portions. The ketone boiled at 177·5°/3 mm., and was not very stable. Neither the phenylhydrazone nor the isomeric pyrazoline could be isolated.

1-*Piperidino-5-(2′-methoxyphenyl)-*Δ^4*-penten-3-one Hydrochloride.*—2-Methoxybenzylideneacetone (Auwers, *Annalen*, 1917, **413**, 279) (10 g.), piperidine hydrochloride (7 g.), and paraformaldehyde (2 g.) in alcohol (15 ml.) were heated together under reflux for 15 mins. After addition of more paraformaldehyde (1 g.), heating was continued for another 15 mins. The solid which separated on thorough cooling and scratching was collected, washed with alcohol and then with ether, and recrystallised from alcohol; white cubes, m. p. 177—178°; yield 13% (Found: C, 65·9; H, 7·4. $C_{17}H_{23}O_2N$,HCl requires C, 65·8; H, 7·7%). *Phenylhydrazone*, yellow powder from alcohol, m. p. 160—162° (Found: N, 10·6. $C_{23}H_{29}ON_3$,HCl requires N, 10·5%).

1-*Phenyl-5-(2′-methoxyphenyl)-3-β-piperidinoethylpyrazoline Hydrochloride.*—The above phenylhydrazone (1·5 g.) was heated with N-hydrochloric acid (15 ml.) on the steam-bath for 20 mins. A clear solution was obtained almost immediately, and on cooling, a green oil separated, which gave a white solid on scratching. Recrystallised from water, this formed a suspension of fine matted crystals which could be filtered off only with difficulty; m. p. 74—75°; yield, 55% (Found: N, 10·2; Cl, 9·2. $C_{23}H_{29}ON_3$,HCl requires N, 10·5; Cl, 8·9%).

By substituting other *o*-alkoxybenzylideneacetones for 2-methoxybenzylideneacetone in the above preparations, the following compounds were obtained: 1-*Piperidino-5-(2′-ethoxyphenyl)-*Δ^4*-penten-3-one hydrochloride*, from 2-ethoxybenzylideneacetone, formed white prisms, m. p. 190°, from alcohol; yield, 30% (Found: C, 66·5; H, 7·6. $C_{18}H_{25}O_2N$,HCl requires C, 66·8; H, 8·0%). *Phenylhydrazone*, yellow powder, m. p. 165—167°, from alcohol (Found: N, 9·9. $C_{24}H_{31}ON_3$,HCl requires N, 10·1%). 1-*Phenyl-5-(2′-ethoxyphenyl)-3-β-piperidinoethylpyrazoline hydrochloride*, from the above phenylhydrazone, separated from water as white needles, m. p. 166°; yield, 60% (Found: N, 10·4; Cl, 8·6. $C_{24}H_{31}ON_3$,HCl requires N, 10·1; Cl, 8·6%).

1-*Piperidino-5-(2′-n-propoxyphenyl)-*Δ^4*-penten-3-one hydrochloride*, from 2-*n*-propoxybenzylideneacetone, crystallised from alcohol in white needles, m. p. 182°; yield, 26% (Found: C, 67·4; H, 7·9. $C_{19}H_{27}O_2N$,HCl requires C, 67·5; H, 8·3%). *Phenylhydrazone*, clusters of yellow needles from alcohol, m. p. 161—162° (Found: N, 9·5. $C_{25}H_{33}ON_3$,HCl requires N, 9·8%). 1-*Phenyl-5-(2′-n-propoxyphenyl)-3-β-piperidinoethylpyrazoline hydrochloride*, white needles

from water; m. p. 193·5°; yield, 75% (Found: N, 10·1; Cl, 8·3. $C_{25}H_{33}ON_3$,HCl requires N, 9·8; Cl, 8·3%).

1-*Piperidino*-5-(2′-n-*butoxyphenyl*)-Δ^4-*penten*-3-*one hydrochloride*, from freshly distilled 2-*n*-butoxybenzylideneacetone, white needles (from alcohol), m. p. 164—165°; yield, 26% (Found: C, 68·1; H, 8·8. $C_{20}H_{29}O_2N$,HCl requires C, 68·2; H, 8·5%). *Phenylhydrazone*, yellow needles from alcohol, m. p. 154—155° (Found: N, 9·8. $C_{26}H_{35}ON_3$,HCl requires N, 9·5%). 1-*Phenyl*-5-(2′-n-*butoxyphenyl*)-3-β-*piperidinoethylpyrazoline hydrochloride*, white needles from water; m. p. 191°; yield, 75% (Found: N, 9·5; Cl, 7·9. $C_{26}H_{35}ON_3$,HCl requires N, 9·5; Cl, 8·0%).

1-*Diethylamino*-5-(2′-n-*butoxyphenyl*)-Δ^4-*penten*-3-*one Hydrochloride*.—By heating freshly distilled 2-*n*-butoxybenzylideneacetone (7·3 g.) and diethylamine hydrochloride (3·7 g.) in alcohol (3 ml.) with two portions of paraformaldehyde (1 g. and 0·5 g.) for 10 mins. after each addition, and cooling and scratching, a sticky solid was obtained. This was freed from liquid by smearing on porous plate, and washed cautiously with alcohol and then with ether. From alcohol, white crystals, m. p. 115—116°, were obtained; yield 5—10%. The *compound* is very soluble in alcohol, but insoluble in ether. It is not hygroscopic (Found: C, 66·4; H, 8·5; N, 4·1. $C_{19}H_{29}O_2N$,HCl requires C, 67·1; H, 8·8; N, 4·1%). In the first attempt to prepare the *phenylhydrazone*, a few mg. of a yellow solid, m. p. 141°, were obtained (Found: N, 9·6. $C_{25}H_{35}ON_3$,HCl requires N, 9·8%); all subsequent attempts gave an unidentified white solid.

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