

64. *Enol Isomerism in the Tropine Series.*

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Two α -hydroxymethyleneacetyltropeines have been isolated and shown to be geometrical isomers about the enolic double bond.

DURING an unsuccessful attempt to prepare atropine by the hydrogenation of α -formylphenylacetyltropeine (*Ia*), we had recourse to Asahina and Nogami's method (*Proc. Imp. Acad., Tokyo*, 1946, **16**, 229) for the preparation of the latter, which had been isolated in yields of about 40% by the action of ethyl formate on phenylacetyltropeine in the presence of sodium methoxide. However, in addition to a relatively insoluble solid product (*Ia*), we isolated, in comparable yield, a yellow-brown oil (*Ib*) which was apparently overlooked by the Japanese authors. Both products are soluble in dilute aqueous sodium hydroxide but insoluble in aqueous sodium hydrogen carbonate, and give an intense violet colour with ferric chloride solution. Both reduce ammoniacal silver nitrate, but only the oil reduces Fehling's solution and gives a copper salt. Hydrolysis with aqueous-alcoholic sodium hydroxide converts both substances quantitatively into tropine and phenylacetic acid, the oil faster than the solid. The compounds give different, crystalline enol benzoates (II), $C_{24}H_{25}O_4N$.

The chemical behaviour of the compounds (*Ia* and *b*) was consistent with their being isomeric α -hydroxymethylenephénylacetyltropeines, and the elaboration of their relationship rested mainly on spectral evidence.

The solid existed entirely in the enolic form (absence of ketonic band in the 1730 cm.^{-1} region; see Table), whereas the oil was probably a tautomeric mixture of enol and aldehyde (bands at 1735 , 1700 , and 1653 cm.^{-1}). As the salt-like properties of the solid seemed to point to strong bonding interaction between the enolic hydroxyl and the tertiary amine group, it was important to ascertain whether this interaction arose from internal or external bonding. Since the compound was virtually insoluble in both carbon tetrachloride and carbon disulphide, infrared spectra were of little value in the 3000 cm.^{-1} region, characteristic of the OH stretching vibrations.

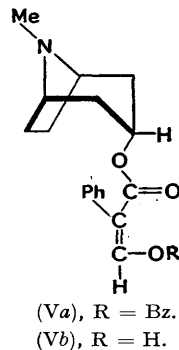
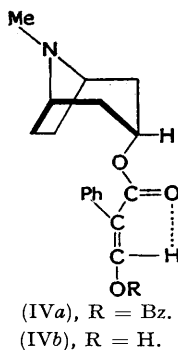
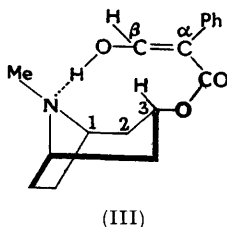
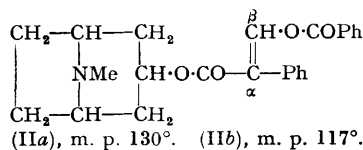
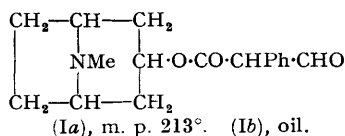
Examination of Catalan models of the compounds (Ia), and approximate calculations using standard bond lengths, have shown that chelation, such as that represented in (III), could occur only (a) if the tropan ring were forced into the boat rather than the normally accepted chair configuration, and (b) if the enolic hydroxyl group were in the *cis*-relation [about the $\alpha\beta$ -double bond; (III)] to the tropan skeleton. This structure would require rotation of $C_{(3)}$ to the same side of the plane as $>NMe$, and change the conformation of the ester group attached to this carbon atom from axial to equatorial.

Although a comparison of the carbon-oxygen stretching bonds of the compound (Ia) in the 1100 — 1200 cm.^{-1} region with those of the benzoates shows a definite hypsochromic shift, comparable to that observed in passing from axial to equatorial conformations in steroids (Page, *J.*, 1955, 2017), assignment of configuration on these grounds is open to doubt since the spectrum of the solid was measured in Nujol mull and because of possible interaction with the enolic hydroxyl group.

Main infrared absorption peaks (cm.⁻¹) (in CCl₄ solution, except where stated).

Substance	Carbonyl	Enol	Ester (C-O)	Substance	Carbonyl	Enol	Ester (C-O)
(Ia) (Nujol) ...	1648	—	1150, 1255	(IIa)	1730, 1700	—	1116, 1240
(Ib)	1735, 1700	1653	—	(IIb)	1730, 1710	—	1120, 1240

The spectra of the enol benzoates, however, gave considerable information. The marked similarity of the curves throughout the range 1650 — 700 cm.^{-1} is consistent with their being geometrical isomers about the enolic double bond. Similar isomerism of enol benzoates has been observed in the case of 2:2-diphenylethyl 2:4:6-trimethylphenyl ketone by Nesmeyanov, Sazanowa, and Vasileva (*Izvest. Akad. Nauk S.S.S.R., Otdel Khim. Nauk*,



1952, 78). The absorption peaks of the two ester-carbonyl groups appear at 1700 and 1730 cm.^{-1} in the benzoate (IIa) and at 1710 and 1730 cm.^{-1} in the isomer (IIb), that at 1700 and 1710 cm.^{-1} being due to the ester attached to $C_{(3)}$ of the tropane skeleton and that at 1730 to the enol benzoate. The slight bathochromic shift (10 cm.^{-1}) of the $\text{C}=\text{O}$ stretching band (cf. IVa) suggests greater hydrogen bonding in this than in the isomer (Va), which is

possible only if the enol-ester group is *trans* about the double bond to the tropan ring [cf. (IVa)]. Since this enol benzoate (IVa) arose from the solid enol (Ia) by treatment with benzoyl chloride and sodium hydroxide, the latter must have the spatial arrangement indicated in (IVb) which cannot be internally chelated, since the enolic hydroxyl is not within bonding distance of the $>\text{NMe}$ group. The compound (Ia) is thus intermolecularly hydrogen bonded, a finding confirmed by its high melting point and salt-like behaviour, by its comparative insolubility in organic solvents, and by its failure to give a copper enolate (Henecka, *Chem. Ber.*, 1948, **81**, 189). The enol benzoate, m. p. 117°, therefore has the spatial structure (Va), and its enolic progenitor contained in the oil (Ib) can be represented by (Vb).

Assignment of the same configuration (probably chair) for the tropan ring in both enol benzoates rests on the similarity of the C—O stretching frequencies attributable to the ester group at $\text{C}_{(3)}$, in the 1100—1200 cm^{-1} region.

EXPERIMENTAL

α -Formylphenylacetyltropine (Ia and b).—Freshly cut sodium (2.9 g.) was emulsified at 140° in anhydrous xylene (100 c.c.), containing one drop of oleic acid. Then anhydrous ethanol (5.8 g.) was added. When most of the sodium had dissolved, a mixture of phenylacetyltropine (32 g.; Hromatka, Csoklich, and Hofbauer, *Monatsh.*, 1952, **83**, 1321) and ethyl formate (11.9 g.) was added dropwise at 15—20°. The mixture was stirred for 3 hr. and poured into 1% sodium hydroxide solution (100 c.c.) with stirring and ice-cooling. The alkaline layer was washed with a little benzene, and the pH adjusted to 7.5 with 10% hydrochloric acid. The precipitated semi-solid product was extracted with chloroform, and the extract washed with saturated sodium chloride solution until neutral. After a few minutes, the crystalline material (5.0 g.) which had been deposited was collected, washed with a little alcohol and ether, and dried *in vacuo*. It had m. p. 212—213° (decomp.).

The filtrate was dried (Na_2SO_4) and concentrated *in vacuo* to the point of crystallization, yielding a second crop of solid (2.0 g.). For analysis, a sample was dissolved in dilute hydrochloric acid at 20°, the solution treated with charcoal and filtered, and dilute aqueous ammonia was added to pH 7.5. The colourless crystals, washed successively with water, alcohol, and ether, and dried *in vacuo*, had m. p. 212—213° (decomp.) (Asahina and Nogami, *loc. cit.*, give m. p. 214°) (Found: C, 70.6; H, 7.6. Calc. for $\text{C}_{17}\text{H}_{21}\text{O}_3\text{N}$: C, 70.9; H, 7.3%). The chloroform filtrate was evaporated under reduced pressure, affording a brown oil (10.4 g.). Both the solid and the liquid product gave a violet colour with ferric chloride solution. The solid product reduced ammoniacal silver nitrate more slowly than did the liquid, and did not reduce Fehling's solution. The liquid product reduced Fehling's solution on boiling and afforded a copper salt on treatment with copper acetate. Repeated attempts to isolate a copper salt of the solid product were unsuccessful.

Alkaline Hydrolysis of the Liquid Isomer.—The oil (2.0 g.) was heated with 20% sodium hydroxide solution (20 c.c.) on a steam-bath for 2 hr., then cooled and thoroughly extracted with chloroform. The extract was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The oily residue of tropine (1.0 g.; b. p. 120°/20 mm.) gave a picrate which, after recrystallization from water, had m. p. and mixed m. p. 285—286° (decomp.). The aqueous layer was acidified with concentrated hydrochloric acid, and the precipitated phenylacetic acid collected, washed with a little cold water, and dried (0.8 g.). A sample recrystallized from light petroleum (b. p. 40—60°) had m. p. and mixed m. p. 75—76°.

Alkaline Hydrolysis of the Solid Isomer.—(i) *With aqueous sodium hydroxide.* The solid (2.0 g.) was heated with 40% sodium hydroxide solution (20 c.c.) on a steam-bath for 2 hr. Extraction with chloroform gave, after drying (Na_2SO_4) and removal of solvent, an oily residue of phenylacetyltropine (1.2 g.). The picrate, after recrystallization from water, had m. p. and mixed m. p. 169—170° (Asahina and Nogami, *loc. cit.*, give m. p. 169°). No phenylacetic acid was isolated from the aqueous layer.

(ii) *With ethanolic potassium hydroxide.* The solid (1.0 g.) was heated with ethanolic potassium hydroxide (50%; 10 c.c.) on a steam-bath for 3 hr. The solution was cooled, diluted with water, and thoroughly extracted with chloroform. The extract, after removal of solvent, afforded a residue of tropine (0.5 g.) which crystallized. It gave a picrate, m. p. and mixed m. p. 286—287° (decomp.). Acidification of the alkaline layer with concentrated hydrochloric

acid afforded phenylacetic acid (0.5 g.), which was washed with a little water and dried. A sample recrystallized from light petroleum had m. p. and mixed m. p. 75—76°.

Enol Benzoates.—(a) The solid (Ia) (2.9 g.) was dissolved in 5% aqueous sodium hydroxide (50 c.c.), and benzoyl chloride (1.4 c.c.) was added dropwise, with stirring. The colourless enol benzoate crystallized after a few minutes. The crystals (2.3 g.) were washed thoroughly with water and dried in a vacuum-desiccator (P_2O_5). Recrystallization from acetone afforded prisms, m. p. 130—131° (Found: C, 73.3; H, 6.6. $C_{24}H_{25}O_4N$ requires C, 73.65; H, 6.4%).

(b) The oil (Ib) (2.9 g.) was dissolved in dry pyridine (20 c.c.), and benzoyl chloride (1.4 c.c.) was added dropwise, with stirring. The mixture was kept at 20° for 24 hr., then poured into ice-water (40 c.c.). The crude enol benzoate which separated slowly (2.1 g.) was recrystallized four times from acetone, affording colourless prisms, m. p. 117—119° (Found: C, 73.45; H, 6.0%). The mixed m. p. with the enol benzoate, m. p. 130—131°, was 100—110°.

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