352. *Piperitone. Part XIII. The Polymorphism of Benzylidene*-dl-*piperitone and some Analogues.*

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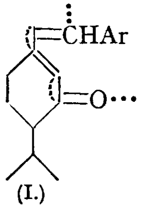
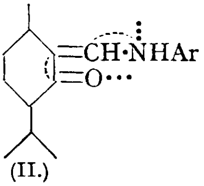
Benzylidene-*dl*-piperitone, when first prepared in Sydney (J., 1921, **119**, 779), was obtained as the α-form; but later preparations (J., 1922, **121**, 574) furnished a β-form, and it was found difficult to reproduce the original α-form until the conditions had been carefully studied. Since this derivative is sometimes used in the recognition of piperitone, it is of practical as well as theoretical interest that numerous recent preparations made in St. Andrews have yielded exclusively a new *γ-benzylidene*-dl-*piperitone,* the α- and the β-form having been unobtainable throughout the experiments. The α- and the β-form pass readily into the γ-form by inoculation; but no transition of the γ-form has yet been observed. Under ordinary conditions the γ-form thus appears to be the most stable of the three forms now known. Some of the main characteristics of these forms are summarised below :

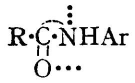
α-Form	⇄	β-Form	→	γ-Form
(Sydney, 1921) very pale yellow, large, monoclinic prisms, m. p. 59—61°.		(Sydney, 1921) pale yellow, large, rhombic prisms, m. p. 63—64°.		(St. Andrews, 1933) faintly yellow, small needles, m. p. 69—70°.

The reason for the failure to obtain the α- and β-forms in the later work is not apparent : it can scarcely be ascribed to differences of temperature prevailing during the crystallisations. It seems clear, however, that the fortuitous presence of a nucleus of the γ-form is sufficient to suppress the production of the α- and β-forms : such nuclei may have been carried from one building to another in the two sets of St. Andrews experiments described below—for example, on the clothes of the operators—in spite of precautions.

The striking nature of the polymorphism of benzylidene-*dl*-piperitone renders noteworthy the complete lack of dimorphism, according to present observations, on the part of similar condensation products of *dl*-piperitone with anisaldehyde, piperonal, salicylaldehyde, opianic acid (Earl and Read, J., 1926, 2072), *p*-dimethylaminobenzaldehyde and furfural (*vide infra*). Since it seemed possible that the occurrence of polymorphism might be conditioned in these instances by the repeated conjugation characteristic of such molecular structures (I), it appeared of interest to examine a series of analogous substances in which the conjugation was continued through a tervalent nitrogen atom (J., 1916, **109**, 1029) instead of a second ethylenic linkage. Suitable substances were found in amino-derivatives of methylenementhone (II) :


(I.)


(II.)


$$\mathrm{R{\cdot}}\underset{\mathrm{O\cdots}}{\mathrm{C}}\mathrm{{\cdot}NHAr}$$
(III.)

m-*Nitroanilinomethylene*-dl-*menthone* was readily obtained in a stable canary-yellow α-form, m. p. 161°, and a labile orange-red β-form, m. p. 110°. Similar forms were observed for p-*nitroanilinomethylene*-dl-*menthone.* The delicate nature of the relationships is indicated by the fact that no clearly defined dimorphism could be established for the corresponding derivatives of *l*-menthone.

The examples of dimorphism observed for substances of the type (II) may be correlated with the polymorphism of certain anilides (III), such as *p*-bromoacetanilide, observed by Chattaway and his collaborators (see, *e.g.*, J., 1915, **107**, 1766; 1916, **109**, 89). It seems likely that polymorphism obtains widely among compounds of such conjugated types, and that failure to recognise the different forms is often due to the difficulty of discovering the conditions requisite for their appearance and to the facility with which a labile form undergoes transformation into a more stable one. In many instances, as indeed with benzylidene-*dl*-piperitone, such transformation may occur unobtrusively, owing to the lack of any obvious colour change: the latest work on this kaleidoscopic substance affords an outstanding example of the subtlety of these interesting phenomena.

EXPERIMENTAL.

*Derivatives of Piperitone.—γ-Benzylidene-*dl*-piperitone.* *l*-Piperitone, obtained from the essential oil of *E. dives* by fractional distillation under diminished pressure and having $\alpha_D - 42°$ (l 1), was condensed with freshly distilled benzaldehyde, precisely as described by Read and Smith (J., 1921, **119**, 785; 1922, **121**, 574). The crude product, after distillation under diminished pressure, melted at 66° (90% yield). When recrystallised from methyl alcohol at room temperature, the material yielded small, doubly terminated needles or prisms, which were not suitable for exact goniometric examination. The colour, a faint yellow, was paler than that of the α- or β-form. The melting point, 69—70°, was unaffected by further recrystallisation. Solutions of the substance were optically inactive (Found: C, 84·9; H, 8·5. $C_{17}H_{20}O$ requires C, 84·9; H, 8·4%). When oxidised by the method of Earl and Read (J., 1926, 2072), this substance, *γ-benzylidene-*dl*-piperitone* (8 g.), yielded α-*iso*propylglutaric acid, m. p. 94° (1·5 g.). *dl*-Piperitone, when treated similarly with benzaldehyde, yielded the same γ-benzylidene-*dl*-piperitone, m. p. 69—70°, and no other substance could be isolated from the product of the reaction.

Similar results were obtained by repeating the preparations from *l*- and *dl*-piperitone in the Department of Physiology, at St. Andrews, *i.e.*, in another building, sterile materials and apparatus being used, and the product seeded with the α-form. In no way was it found possible to obtain either α- or β-benzylidene-*dl*-piperitone in the course of repeated experiments carried out in the two laboratories concerned.

When concentrated solutions in methyl or ethyl alcohol of α- or β-benzylidene-*dl*-piperitone (prepared in Sydney, in 1921) were inoculated with the γ-form, all the material separated in the γ-form. A similar result attended the inoculation of solutions of the γ-form with crystals of the α- or β-form. Moreover, molten γ-benzylidene-*dl*-piperitone crystallised in the γ-form when seeded with the α- or β-form.

After being kept for some years, crystals of the α-form deepen in colour and become opaque; the surface vitrifies, and small nodules of a vitreous material appear on the sides of the containing vessel. The β-form, however, when preserved under similar conditions, remains unaltered; the crystals retain their transparency, and the facets their smoothness and lustre. A similar statement applies to the γ-form.

p-*Dimethylaminobenzylidene-*dl*-piperitone.* A solution of *dl*-piperitone (10 g.) and *p*-dimethylaminobenzaldehyde (9·8 g., 1 mol.) in absolute alcohol (20 c.c.) was mixed with a solution of sodium (0·4 g.) in absolute alcohol (20 c.c.) and kept for 4 days at room temperature. The product was poured into water and extracted with chloroform. The chloroform solution deposited long, flat prisms, m. p. 116—117°, with a deep orange colour and a pronounced lustre (Found: C, 80·1; H, 8·9. $C_{19}H_{25}ON$ requires C, 80·5; H, 8·9%). The *derivative* was soluble in dilute mineral acids, forming pale yellow solutions, and was reprecipitated upon basification.

*Furfurylidene-*dl*-piperitone*, prepared in a similar way from furfural and *dl*-piperitone, was first obtained as a brown, crystalline powder. Treatment in alcoholic solution with norit, followed by crystallisation from aqueous alcohol, yielded long, orange-brown prisms, m. p. 66° (Found: C, 78·3; H, 8·0. $C_{15}H_{18}O_2$ requires C, 78·2; H, 7·9%).

Neither of these derivatives afforded any indications of dimorphism when recrystallised from a selection of organic solvents under varied conditions.

Derivatives of dl-*Menthone.—Hydroxymethylene-*dl*-menthone.* *dl*-Piperitone (40 g.) was reduced with sodium (50 g.) in absolute alcohol (450 c.c.) to crude *dl*-menthols (36 g.), which when oxidised according to Beckmann (*Annalen*, 1889, **250**, 325) gave crude *dl*-menthone (J., 1926, 2210; 1927, 1278; *Chem. Reviews*, 1930, **7**, 20). This was converted by the method of Bishop, Claisen, and Sinclair (*Annalen*, 1894, **281**, 394) into *hydroxymethylene-*dl*-menthone*, a limpid, yellow oil, b. p. 120—122°/14 mm. (Found: C, 72·1; H, 9·9. $C_{11}H_{18}O_2$ requires C, 72·5; H, 10·0%).

*Anilinomethylene-*dl*-menthone.* When aniline (0·9 g.), dissolved in 30% acetic acid, was mixed on the water-bath with a hot solution of hydroxymethylene-*dl*-menthone (1·8 g.), a reddish-brown oil separated. After remaining overnight, the mixture was poured into water, and the oil was extracted with ether. When kept for a fortnight, the oil yielded crystalline material, which upon recrystallisation from methyl alcohol formed faintly yellow, glistening needles, m. p. 103° (Found: C, 79·0; H, 9·2. $C_{17}H_{23}ON$ requires C, 79·3; H, 9·0%). The *substance* was not obtained in polymorphic forms, but it readily reverted to a thick syrupy liquid when separating from organic solvents.

The derivatives described below were prepared similarly, except that sometimes the concentration of the acetic acid was increased. Methylanilinomethylene-*dl*-menthone was isolated as a yellow oil which gradually became reddish-brown. *o*-Nitroanilinomethylene-*dl*-menthone was a thick red oil. m-*Nitroanilinomethylene*-dl-*menthone* was readily obtained in theoretical yield as a dark red oil which changed to orange crystals, m. p. 118—121°, upon the addition of alcohol on the water-bath. Upon careful recrystallisation from hot absolute alcohol, the first separation obtained during slow cooling consisted of canary-yellow needles of the α-form, m. p. 161° (Found: C, 67·7; H, 7·2. $C_{17}H_{22}O_3N_2$ requires C, 67·5; H, 7·3%); these were succeeded by a smaller quantity of orange-red prisms of the β-*form*, m. p. 110° with preliminary softening (Found: C, 67·5; H, 7·1%). The α-form may readily be obtained pure by warming a mixed separation of the two kinds of crystals in the original mother-liquor: the β-form then dissolves, leaving the α-form. When recrystallised from alcohol, the α-form preserves its characteristics. The pure β-form is best obtained by boiling a concentrated alcoholic solution of the substance in a flask, so as to free it from all nuclei. When the flask is closed with a wad of cotton-wool and left undisturbed, a separation of glistening orange-red needles usually ensues. Both forms, when melted and allowed to cool in a sterile tube, resolidify to the β-form, which is the labile modification under ordinary conditions.

p-*Nitroanilinomethylene*-dl-*menthone* separated originally, in theoretical yield, as an orange oil; when kept for a few hours, this changed into canary-yellow crystals, m. p. 120—132°. Recrystallisation from hot alcohol furnished canary-yellow clusters of minute soft needles of the α-form, m. p. 147° (Found: C, 67·5; H, 7·1%). The mother-liquors from such recrystallisations, when kept for several days at room temperature, deposited hard, orange-red prisms, which gradually assumed an irregular shape, with feather-like striations; this β-form melted at 117° (Found: C, 67·6; H, 7·2%). A hot, sterile alcoholic solution of the α-form, upon cooling, deposited nothing except soft canary-yellow needles for 2 days, after which a smaller deposit of hard, orange-red prisms appeared. A hot solution of the β-form, when cooled slowly, deposited crystals of the same kind, but after 4 days small clusters of minute soft needles began to form on the large orange-red crystals.

β-*Naphthylaminomethylene*-dl-*menthone* was obtained as a reddish syrup, which slowly crystallised in the course of a fortnight. It separated from light petroleum in long, fine needles, m. p. 58—61°, and was exceedingly soluble in organic solvents. No indications of dimorphism were observed in this case (Found: C, 81·8; H, 8·3. $C_{21}H_{25}ON$ requires C, 82·0; H, 8·2%).

Derivatives of l-*Menthone.*—Hydroxymethylene-*l*-menthone, prepared (*Annalen*, 1894, **281**, 394) from *l*-menthone with $\alpha_D^{16°} - 26·00°$ (*l* 1), had b. p. 129—131°/17 mm., 116—117°/10 mm., $\alpha_D^{16°} + 16·89°$ (*l* 1). *p*-Nitroanilinomethylene-*l*-menthone was a thick, dark red oil, which would not crystallise. m-*Nitroanilinomethylene*-l-*menthone* separated from alcohol in clusters of glistening needles, m. p. 104° (Found: C, 67·4; H, 7·2%); the deep orange-red colour became somewhat deeper when the substance was kept for some days in diffused light. No clearly defined dimorphism could be established. The orange-red crystals were reproduced during recrystallisation from hot or cold alcoholic solutions under various conditions. In one instance, a crop of crystals was partly dissolved by warming in contact with the original mother-liquor, and the residue when collected and washed with a little ether gave bright orange needles which did not melt completely until reaching 110°. A specimen of the substance precipitated from alcoholic solution by the addition of water melted at 104°. This derivative, like the parent substance, although prepared ultimately from *l*-menthone, was dextrorotatory, with $[\alpha]_D^{16°} + 65·7°$ (*c* 3·3, alcohol). No mutarotation was evident.

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