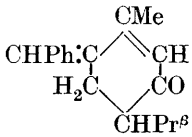
CCLXXVII.—*Piperitone. Part VIII. The Condensation of Piperitone with Aldehydes.*

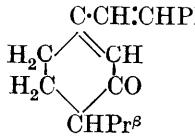
By JOHN CAMPBELL EARL and JOHN READ.

THE ease with which piperitone undergoes condensation with benzaldehyde (J., 1921, **119**, 784) suggested an extension of the reaction to other aldehydes, more especially in view of the striking nature of the dimorphism exhibited by the optically inactive benzylidene derivative (J., 1922, **121**, 574), which appeared to merit further study. In the present communication it is shown that piperitone condenses equally readily with anisaldehyde and also with piperonal. The resulting derivatives, owing to the great facility with which they crystallise, are even more suitable than benzylidene-*dl*-piperitone for the identification of the ketone. Piperitone also undergoes condensation with salicylaldehyde and with opianic acid in a similar manner. In no case, however, was dimorphism evident on the part of the product. Owing to the racemisation of the optically active ketone when condensed with aldehydes in presence of alkali, attempts were also made to effect the reaction in an acid medium, in the hope that the corresponding optically active derivatives might result in this way, a crystallographic examination of the optically active benzylidene derivatives being particularly desirable on account of the exceptional characteristics of benzylidene-*dl*-piperitone. Although condensation was successfully accomplished in this manner, the process was still accompanied by complete racemisation. The condensing action of aqueous hydrochloric acid on mixtures of piperitone with aldehydes seems to be general, but the yields are small. Since neither of these methods of condensation furnished an optically active product, the opianylidene derivative was prepared with the ultimate aim of achieving the optical resolution of the acidic product by means of an optically active base; the salts so far examined, however, show little tendency to crystallise.

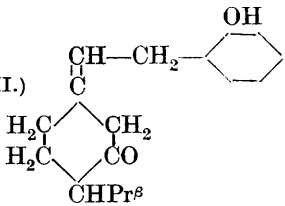
As regards the constitution of these piperitone derivatives, it was originally suggested by Simonsen (J., 1921, **119**, 1648) that condensation with benzaldehyde occurs in the 6-position (formula I), owing to the activation exerted by the adjacent ethylenic linking. This suggestion was adopted in a subsequent discussion of the constitution of piperitone (Read, Smith, and Hughesdon, J., 1924, **125**, 129), although for the purpose of the argument it was unnecessary to decide whether condensation actually affects position 6 or position 7. A further study of this question has now indicated that condensation occurs, in fact, in position 7, and not in position 6.

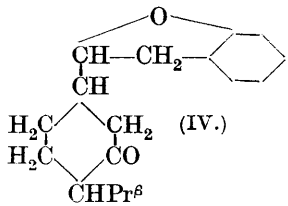
The reaction, however, may still be attributed to the activating influence of the Δ^1-ethylenic linking of piperitone, or, more precisely, to the system C:C·CO, which thus seems to exert its maximum effect in the side chain rather than in the ring. The constitution (II) now advanced for benzylidenepiperitone is based upon the observation that when carefully oxidised with a cold solution of potassium permanganate in acetone this substance yields α-*iso*propylglutaric acid, instead of *iso*propylsuccinic acid as required by formula (I). In the latter case, the production of α-*iso*propylglutaric acid would be possible only by virtue of a simultaneous removal of the benzylidene group by hydrolysis, a process which is extremely unlikely in view of the nature of the reagent and the great stability of benzylidenepiperitone towards hydrolysing agents (J., 1922, **121**, 577). The presumed 6-benzylidene-*dl*-piperitone, 6-benzyl-*dl*-*iso*menthone, 6-benzyl-*dl*-*iso*menthol and 2-benzylidene-6-benzyl-*dl*-*iso*menthone (J., 1924, **125**, 134) must accordingly be regarded as 7-benzylidene-*dl*-piperitone (II), 7-benzyl-*dl*-*iso*menthone, 7-benzyl-*dl*-*iso*menthol, and 2-benzylidene-7-benzyl-*dl*-*iso*menthone, respectively.

(I.) 

 (II.)

Since similar considerations may be applied to the products of condensation of piperitone with other aldehydes, formed in the ways now described, the two isomeric dihydro-derivatives of salicylidenepiperitone mentioned in the experimental part of this paper are probably to be formulated as follows, (III) being soluble and (IV) insoluble in aqueous alkali.

(III.) 

 (IV.)

EXPERIMENTAL.

Anisylidene-dl-*piperitone*, $C_{10}H_{14}O$:CH·C_6H_4·OMe.—*dl*-Piperitone (10 g.) and anisaldehyde (9 g., 1 mol.) were dissolved in absolute alcohol (20 c.c.) and mixed with a cold solution of sodium (0·4 g., 0·25 mol.) in absolute alcohol (20 c.c.). After keeping for a week,

the solution was poured into an excess of water and made slightly acid with sulphuric acid. The ensuing oily separation of anisylidene-*dl*-piperitone solidified in a few minutes to a crystalline mass (12·8 g.). The derivative is readily soluble in chloroform or benzene, and somewhat less soluble in alcohol or warm ligroin. When recrystallised from alcohol it forms pale yellow crystals, m. p. 98°. No dimorphism was observed after repeated recrystallisation under different conditions (Found: C, 80·1; H, 8·2. $C_{18}H_{22}O_2$ requires C, 79·9; H, 8·25%). The appended crystallographic report was kindly supplied by Dr. Marie Bentivoglio, of the Department of Geology, University of Sydney:

The crystals, which are doubly terminated, vary in habit, being either long prisms—elongated in the direction of the *c* axis—or short crystals equally developed in the directions of the three axes. They are transparent and light yellow in colour, and have smooth faces, with good lustre, which give satisfactory reflections. The prism zone contains prominent *a*(100) and *b*(010) faces and occasionally two of the primary prisms *m*(110); but four of these faces on one crystal were not observed. The bipyramid *o*(124) is always well developed, and often the primary brachydomal prism *d*(011) is present as a very small face giving poor reflections. There is a distinct cleavage parallel to *b*(010).

Crystal system: Rhombic normal.

Axial ratios: $a : b : c = 0{\cdot}91900 : 1 : 0{\cdot}82044$.

The table of angles is given below:

Angle.	No. of measurements.	Limits.	Mean.	Calculated.
ab-100 : 010	15	89° 55′— 90° 07′	90° 01	90° 00′
bm-010 : 110	4	47 09 — 47 18	47 14	47 25
bd-010 : 011	7	50 30 — 50 49	50 39	50 38
oo-124 : $\bar{1}24$	10	56 58 — 57 22	57 12	57 06
oo-124 : $1\bar{2}4$	10	122 40 —122 56	122 46	122 54
oo-124 : $\bar{1}\bar{2}4$	10	49 52 — 50 10	49 58	50 04

The same derivative was also prepared by leaving an equimolecular mixture of *l*- or *dl*-piperitone and anisaldehyde in contact with about three times the weight of concentrated hydrochloric acid for 3 weeks at the ordinary temperature, with occasional shaking. Upon inoculation with crystalline material prepared as above, the gummy product became partly crystalline. The yield of the purified derivative was small, amounting only to about 12% of that recorded above.

Salicylidene-dl-*piperitone*, $C_{10}H_{14}O{:}CH{\cdot}C_6H_4{\cdot}OH$.—The customary method could not be used in this instance, on account of the sparing solubility of the sodium derivative of salicylaldehyde in absolute alcohol. A solution of salicylaldehyde (16 g.) in 10%

aqueous sodium hydroxide was accordingly stirred vigorously with an equimolecular proportion of *dl*-piperitone (20 g.) on a boiling water-bath for 10 hours. The reaction-product was then steam distilled before and after acidification, in order to remove unchanged piperitone (7 g.) and salicylaldehyde, respectively. The residual dark resin when separated and dissolved in hot alcohol yielded successive fractions of crystalline material (8·4 g.); after repeated recrystallisation from the same solvent the product maintained its crystalline characteristics, forming small pale yellow crystals, m. p. 177° (Found: C, 79·6; H, 7·8. $C_{17}H_{20}O_2$ requires C, 79·6; H, 7·9%). Salicylidene-*dl*-piperitone is readily soluble in hot alcohol, and sparingly soluble in cold alcohol, benzene or ether. It forms an orange-yellow solution in sodium hydroxide, but does not dissolve in aqueous sodium bicarbonate.

The same derivative was formed by condensation in presence of concentrated hydrochloric acid, according to the method outlined above for anisylidene-*dl*-piperitone; the yield in this instance was only slightly less than that afforded by the alkaline condensation.

When reduced with zinc dust and alkali, salicylidene-*dl*-piperitone yielded two crystalline products, which appeared to be isomeric dihydro-derivatives having the formula $C_{17}H_{22}O_2$. The first of these, probably formed by normal reduction of the conjugated system in accordance with Thiele's theory, was soluble in aqueous alkali, like the original derivative; it showed evidence of unsaturation, and was not particularly stable. The isomeric reduction product was insoluble in aqueous alkali, and was much more stable than the first product; in this instance the molecule was apparently characterised by the presence of a coumaran ring. These interesting reduction products will form the subject of further study.

Piperonylidene-dl-*piperitone*, $C_{10}H_{14}O{:}CH{\cdot}C_7H_5O_2$.—*dl*-Piperitone (10 g.) and piperonal (10 g., 1 mol.) were dissolved in absolute alcohol (20 c.c.) and mixed with a cold solution of sodium (0·4 g., 0·25 mol.) in absolute alcohol (20 c.c.). Upon keeping the solution at the ordinary temperature crystals soon started to separate, and after 2 days the mixture was poured into water. The crystalline product (16·2 g.) when recrystallised from alcohol melted at 128° (Found: C, 75·8; H, 7·0. $C_{18}H_{20}O_3$ requires C, 76·0; H, 7·1%). Piperonylidene-*dl*-piperitone consists of pale yellow, flaky crystals with a reddish tinge, which persists throughout repeated recrystallisations from alcohol but disappears after recrystallisation from benzene. Apart from this behaviour, no indication of dimorphism was observed. The derivative is readily soluble in benzene or chloroform, and moderately soluble in warm alcohol and ligroin.

Opianylidene-dl-*piperitone*, $C_{10}H_{14}O{:}CH{\cdot}C_6H_2(OMe)_2{\cdot}CO_2H$. — A

solution of sodium (1·9 g.) in absolute alcohol (40 c.c.) was added to a slightly warm solution of *dl*-piperitone (10 g.) and opianic acid (14 g.) in absolute alcohol (40 c.c.). After being kept for 5 days at the ordinary temperature, the mixture was poured into water, the unchanged piperitone being then removed by extraction with ether. When freed from ether and acidified, the clear aqueous solution gave a yellow syrupy precipitate which gradually became crystalline when cooled in ice. Recrystallisation from alcohol furnished pale yellow crystals (8·2 g.), which melted at 157° when heated rapidly. The substance showed no tendency to crystallise in dimorphic forms (Found: C, 69·3; H, 7·2; *M*, by titration, 335. $C_{20}H_{24}O_5$ requires C, 69·7; H, 7·0%; *M*, 344). The derivative is sparingly soluble in hot benzene, but it dissolves readily in chloroform or hot alcohol and also in ammonia or sodium carbonate solutions. It forms insoluble lead, silver, and calcium salts: the *calcium* salt, which is anhydrous, was analysed [Found: Ca, 5·4. $(C_{20}H_{23}O_5)_2Ca$ requires Ca, 5·5%].

Oxidation of Benzylidene-dl-*piperitone*.—To a solution of benzylidene-*dl*-piperitone (8 g.) in acetone (50 c.c.), cooled to 0°, was added with stirring in the course of 3·5 hours a solution of potassium permanganate (20 g.) in a mixture of acetone (400 c.c.) and water (90 c.c.). The resulting precipitate was separated, washed with acetone, dried, and dissolved in a cooled mixture of concentrated sulphuric acid (50 c.c.) and water (350 c.c.). The product obtained from the ether extract of this solution crystallised when kept in a desiccator (2·2 g.). When recrystallised from the minimum quantity of boiling water, it formed colourless crystals, m. p. 94°, and was diagnosed as α-*iso*propylglutaric acid [Found: C, 54·9; H, 7·9; *M*, by titration, 174. $C_6H_{12}(CO_2H)_2$ requires C, 55·2; H, 8·1%; *M*, 174]. The anhydride had m. p. 51—52°, and the anil m. p. 160° (compare Perkin, J., 1896, **69**, 1495). The acetone filtrate in the original oxidation appeared to contain nothing beyond benzaldehyde and some unchanged benzylidene-*dl*-piperitone.

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