42. *Researches in the Carvone Series. Part IV. Optically Active Carvotanacetols and Carvotanacetylamines.*

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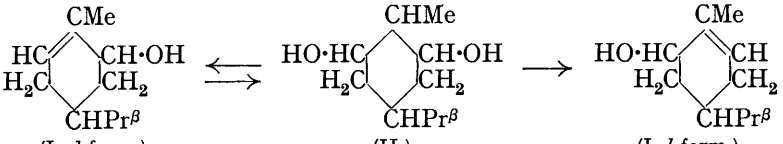
NEITHER of the two stereoisomeric carvotanacetols related to *d* (or *l*)-carvotanacetone has hitherto been isolated, although an impure carvotanacetol has been prepared by oxidising carvomenthene with selenium dioxide (Tabuteau, *Compt. rend.*, 1935, **200**, 244). It is now shown that Ponndorf's reduction (*Z. angew. Chem.*, 1926, **39**, 138) produces capricious results when applied to *d*-carvotanacetone (cf. J., 1935, 1140). An apparently pure d-*carvotanacetyl* p-*nitrobenzoate*, m. p. 93·5—94°, $[\alpha]_D$ + 85·0°, prepared from the reduction product, yielded upon hydrolysis a d-*carvotanacetol* with α_D + 100·5° (*l* 1); the pure *p*-nitrobenzoate of the stereoisomeric carvotanacetol, m. p. 60—62°, $[\alpha]_D$ — 51·3°, also appears to have been isolated. Unexpectedly, the above *d*-carvotanacetol (I) was found to undergo partial racemisation in presence of acids. This striking phenomenon, shown by a substance whose molecule contains two dissimilar asymmetric centres in a ring system, may be due either (1) to hydration to the 2 : 6-diol (II),* followed by a two-way dehydration, as indicated below,

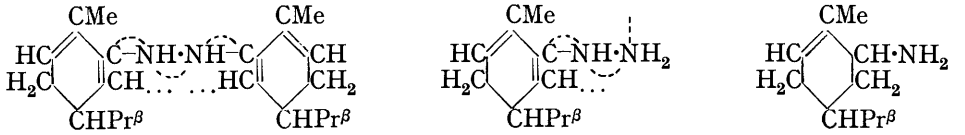


(I, *d*-form.) (II.) (I, *l*-form.)

or (2) to anion migration, which might apply to the nitrobenzoates as well as to the free alcohols (cf. such references as Burton and Ingold, J., 1928, 90; Burton, J., 1928, 1650; 1930, 248; 1934, 1268—for which we are indebted to Dr. J. Walker). Further, we find that *l-trans*-carveol (J., 1934, 236) and *l*-Δ^4-menthen-3-ol (unpublished) suffer partial racemisation in presence of acids, as might be inferred from their structural likeness to the carvotanacetols.

It is striking that this carvotanacetol showed no tendency to undergo dehydration to α-phellandrene, like the structurally related αβ-unsaturated piperitols (J., 1930, 2770; 1934, 308). Indeed, the investigations recorded in this paper and the preceding one serve to illustrate how little is known of the behaviour of unsaturated monocyclic alcohols.

When treated with hydrazine, *d*-carvotanacetone reacted very similarly to *l*-piperitone (J., 1930, 2770), yielding a viscid product which appeared to consist of a mixture of the azine and the hydrazone. Upon reduction with tin and acetic acid, this gave a mixture of carvotanacetylamines (V), which, however, differed from the corresponding piperitylamines (*ibid.*) in being optically active. This interesting result confirms the mechanism postulated earlier (J., 1934, 310) for the reduction of piperitone azine, since in the present instance the supposed lactam form of the azine (III), or hydrazone (IV), would not lose its asymmetry :



(III.) (IV.) (V.)

A similar mixture of two stereoisomeric carvotanacetylamines was obtained by reducing *d*-carvotanacetone oxime (Harries and Johnson, *Ber.*, 1905, **38**, 1832). The crude base, having α_D + 121·46° (*l* 1), when treated with *d*-tartaric or oxalic acid readily yielded pure d-*carvotanacetylamine*, with α_D + 169·54°. The benzoyl derivative of this base had m. p. 97—98°, $[\alpha]_D$ + 214·0° (*c* 2·0, chloroform). The benzoyl derivative of the stereoisomeric

* The diagram applies to the two *dl*-forms of the asymmetric *trans*-2 : 6-diol : both forms of the *cis*-2 : 6-diol would be symmetric.

base was also isolated, and this derivative had m. p. 165°, $[\alpha]_D$ — 87·5°. No stereochemically pure carvotanacetol has as yet been prepared from the above *d*-carvotanacetylamine by methylation or through the action of nitrous acid (cf. J., 1930, 2779).

Experimental.

The Reduction of d-*Carvotanacetone to Carvotanacetols.*—*d*-Carvone from caraway oil was hydrogenated with the aid of a selective catalyst until 1 mol. of hydrogen had been absorbed. Purification of the product by means of the bisulphite compound yielded a pale yellow, mobile oil with an odour resembling that of *d*-carvone; the main fraction, distilling at 98—99°/16 mm., gave constants, $n_D^{21°}$ 1·4791, $[\alpha]_D^{19°}$ + 55·2°, agreeing well with the published data for *d*-carvotanacetone. The ketone reacted with semicarbazide acetate in cold aqueous alcoholic solution, yielding a semicarbazone (80% yield) with m. p. 170—171°, $[\alpha]_D$ + 77·0° (*c* 2·0 chloroform). After several recrystallisations this product furnished large colourless prisms, m. p. 173—174°, $[\alpha]_D$ + 80·0°. When hydrolysed with hot 20% aqueous oxalic acid, the derivative yielded *d*-carvotanacetone with b. p. 105—106°/21·5 mm., $n_D^{20°}$ 1·4796, $[\alpha]_D$ + 58·3°. The purified oxime had m. p. 76—77°, $[\alpha]_D$ + 22·5° (*c* 2·0, chloroform). The 2 : 4-dinitrophenylhydrazone formed scarlet needles, m. p. 191—192°.

Upon reduction with dry *iso*propyl alcohol and aluminium *iso*propoxide for 8—9 hours, according to the method of Ponndorf (*Z. angew. Chem.*, 1926, **39**, 141), *d*-carvotanacetone having $[\alpha]_D^{19°}$ + 55·2° gave a product which distilled mainly at 108—109°/19·5 mm., and had $n_D^{20°}$ 1·4800, $\alpha_D^{18°}$ + 86·0° (*l* 1, homogeneous). The derived 3 : 5-dinitrobenzoate was a solid with $[\alpha]_D$ + 61·0° (*c* 2·0, chloroform), which could not be effectively recrystallised. The crude *p*-nitrobenzoate had m. p. 87—90°, $[\alpha]_D$ + 76·5°; when it was recrystallised four times from methyl alcohol, the values for the resulting d-*carvotanacetyl* p-*nitrobenzoate* reached constancy at m. p. 93·5—94°, $[\alpha]_D$ + 85·0° (Found : C, 67·3; H, 6·9. $C_{17}H_{21}O_4N$ requires C, 67·3; H, 6·9%). Hydrolysis with boiling 3·5% methyl-alcoholic potassium hydroxide yielded d-*carvatanacetol* as a somewhat viscid oil, b. p. 101°/13 mm., $n_D^{20°}$ 1·4800, $\alpha_D^{17°}$ + 100·5° (*l* 1, homogeneous), $d_4^{17°}$ 0·9307, $[R_L]_D$ 47·1 (calc. for $C_{10}H_{18}O$, 1⌐, 47·3).

Oxidation of the above alcohol with Beckmann's mixture furnished a ketone with b. p. 96·5°/14 mm., $n_D^{19°}$ 1·4800, $\alpha_D^{17°}$ + 40·7° (*l* 1, homogeneous). This specimen of *d*-carvotanacetone thus contained some *dl*-carvotanacetone, and fractional crystallisation of the derived semicarbazone furnished a fraction with m. p. 180—181°, $[\alpha]_D$ + 3·7° (*c* 2·0, chloroform). Pure *dl*-carvotanacetone semicarbazone, prepared from the *dl*-ketone, crystallised in prisms, m. p. 180°, and *dl*-carvotanacetone oxime in stout needles, m. p. 94—95°.

In tracing the point at which the partial racemisation had occurred, it was found that the optical rotation of *d*-carvotanacetone was not disturbed by submitting the ketone to the conditions of the Beckmann oxidation at 60°. The optical rotation of the mixture of alcohols obtained in a Ponndorf reduction of this ketone, and having $\alpha_D^{18°}$ + 77·3° (*l* 1, homogeneous), also remained unaltered when the mixture was kept in contact with 2*N*-sodium hydroxide solution at 90° for 15 minutes. When this treatment was repeated with 12% hydrochloric acid, however, the optical rotation fell from $\alpha_D^{18°}$ + 77·3° to + 12·8°; a small quantity of *dl*-α-phellandrene was produced during this treatment. Another specimen of this mixture of carvotanacetols when oxidised with Beckmann's mixture yielded *d*-carvotanacetone with $\alpha_D^{18°}$ + 44·0°: since the original ketone used in the Ponndorf reduction had $\alpha_D^{18°}$ + 52·0°, it is evident that partial racemisation occurs during the oxidation of these carvotanacetols with chromic acid. It was shown further that the mixture of optically active carvotanacetols could be esterified in dry pyridine with 3 : 5-dinitrobenzoyl chloride and regenerated by alkaline hydrolysis without loss of optical rotation, provided that the reaction mixtures were not permitted to become acidic at any stage of the operations.

The above specific rotatory powers were the highest observed for *d*-carvotanacetyl *p*-nitrobenzoate and the corresponding *d*-carvotanacetol. Certain specimens of the ester with somewhat lower optical rotations failed to yield higher values upon repeated recrystallisation, thus indicating the possible formation of mixed crystals.

In one experiment, a specimen of *d*-carvotanacetone having α_D + 54·44° (*l* 1), which had been regenerated from the purified semicarbazone (see above), yielded in the Ponndorf reduction a mixture of carvotanacetols with b. p. 113—114°/22 mm., $n_D^{18°}$ 1·4818, α_D + 50·89° (*l* 1). The crude *p*-nitrobenzoate had m. p. 50—80°, $[\alpha]_D$ — 1·0° (*c* 2·0, chloroform); six successive recrystallisations from methyl alcohol yielded needles, m. p. 93—94°, $[\alpha]_D$ + 85·2° (*c* 2·0 chloroform), identical with the *d*-carvotanacetyl *p*-nitrobenzoate already described. The first two mother-

liquors deposited needles, m. p. 57—63°, $[\alpha]_D$ — 44·2°; three successive recrystallisations from methyl alcohol yielded an isomeric *carvotanacetyl* p-*nitrobenzoate*, m. p. 60—62°, $[\alpha]_D$ — 51·3° (Found : C, 67·4; H, 6·8%). The crude 3 : 5-dinitrobenzoate, having m. p. 68—75°, $[\alpha]_D$ + 7·0°, after four recrystallisations from methyl alcohol yielded small yellow plates of a *carvotanacetyl* 3 : 5-*dinitrobenzoate*, m. p. 88·5—90°, $[\alpha]_D$ — 33·3° (Found : C, 58·7; H, 5·7. $C_{17}H_{20}O_6N_2$ requires C, 58·6; H, 5·8%). The mother-liquors yielded a white powder. The above Ponndorf reduction, furnishing a mixture of carvotanacetols of exceptionally low rotatory power, could not be repeated.

The Preparation of Carvotanacetylamines from d-*Carvotanacetone*.—(1) *d*-Carvotanacetone oxime (50 g.), having $[\alpha]_D$ + 22·5° (*c* 2·0, chloroform), was dissolved in absolute alcohol (100 c.c.) and mixed at 0° with glacial acetic acid (200 c.c.). Pure zinc powder (80 g.) was introduced gradually (2 hours) into the stirred mixture, which was kept below 5°, and after an hour more acetic acid (25 c.c.) was added (cf. Harries and Johnson, *Ber.*, 1905, **38**, 1832). Stirring was continued before (1 hour) and after (2½ hours) removing the mixture from the ice-bath. The temperature rose spontaneously to 60°, and the reaction was completed by heating the mixture on a boiling water-bath (1 hour). The product was cooled and filtered, the residue being washed with water and methyl alcohol. The ice-cooled filtrate was basified with concentrated sodium hydroxide solution and distilled in steam. The acidified distillate was extracted twice with ether, basified, saturated with potassium chloride, and again extracted twice with ether. The last extracts, when dried and distilled, yielded the crude base (30 g.) with b. p. 97°/17·5 mm., $n_D^{18°}$ 1·4820, $\alpha_D^{15°}$ + 121·46° (*l* 1, homogeneous). The crude hydrogen *d*-tartrate (143 g.) had m. p. 95—105°, $[\alpha]_D$ + 68·8° (*c* 2·0, water); after four recrystallisations from ethyl acetate–methyl alcohol, flat needles (52 g.) of d-*carvotanacetylamine hydrogen* d-*tartrate* were obtained, with m. p. 141—142°, $[\alpha]_D^{15°}$ + 97·5° (*c* 2·0, water), $[M]_D$ of basic ion + 249° (Found : C, 55·4; H, 8·3. $C_{14}H_{25}O_6N$ requires C, 55·4; H, 8·3%). The crude hydrogen oxalate had m. p. *ca.* 170°, $[\alpha]_D^{15°}$ + 75·0° (*c* 2·0, water); after three recrystallisations from ethyl acetate–methyl alcohol, minute needles of d-*carvotanacetylamine hydrogen oxalate* were obtained, with m. p. 205°, $[\alpha]_D^{15°}$ + 102·3° (*c* 2·0, water), $[M]_D$ of basic ion + 248° (Found : C, 59·6; H, 8·6. $C_{12}H_{21}O_4N$ requires C, 59·3; H, 8·5%). The original mother-liquors from the above recrystallisations yielded thick syrups upon evaporation. Pure *d*-carvotanacetylamine was obtained by treating the above pure hydrogen *d*-tartrate with aqueous sodium hydroxide. A colourless mobile liquid with a basic odour, it absorbed carbon dioxide rapidly from the air, and had b. p. 93°/16·5 mm., $d_{4°}^{15°}$ 0·8917, $n_D^{15°}$ 1·4815, $n_D^{16·6°}$ 1·4810, $\alpha_D^{15°}$ + 169·54°, $[\alpha]_D^{15°}$ + 190·1° (*l* 1, homogeneous), $[R_L]_D$ 48·92 (calc. for $C_{10}H_{19}N$, 1 ⟌, 49·13).

Acetyl-d-*carvotanacetylamine* crystallised in flat needles, m. p. 112°, $[\alpha]_D$ + 155·3° (*c* 2·0, chloroform) (Found : C, 73·9; H, 10·8. $C_{12}H_{21}ON$ requires C, 73·8; H, 10·8%). *Benzoyl*-d-*carvotanacetylamine* formed long needles, m. p. 97—98°, $[\alpha]_D$ + 214·0° (*c* 2·0, chloroform) (Found : C, 79·7; H, 8·8. $C_{17}H_{23}ON$ requires C, 79·3; H, 9·0%). The hydrogen succinate was obtained crystalline, but the hydrogen phthalate formed a viscid syrup.

(2) When treated with hydrazine, according to the method of Read and Storey (J., 1930, 2780), *d*-carvotanacetone gave a fairly mobile, pale yellow syrup having $[\alpha]_D^{17°}$ + 11·5° (*c* 2·3, chloroform) (Found : C, 73·1; H, 10·5; N, 14·8%). After remaining at the ordinary temperature for 14 days the material had become much more viscid and the colour had deepened to a dark red-brown; the value of $[\alpha]_D^{17°}$ had meanwhile changed to — 47·9° (Found : C, 73·9; H, 10·2; N, 13·6. Carvotanacetone hydrazone, $C_{10}H_{18}N_2$, requires C, 72·3; H, 10·8; N, 16·9. Carvotanacetone azine, $C_{20}H_{32}N_2$, requires C, 80·0; H, 10·8; N, 9·3%).

When the freshly prepared material was reduced by the method of Read and Storey (*loc. cit.*) it gave a 25% yield of a base resembling that obtained by the reduction of *d*-carvotanacetone oxime and having b. p. 100—102°/24·5 mm., $n_D^{21°}$ 1·4792, $\alpha_D^{17°}$ + 106·3° (*l* 1, homogeneous). The crude benzoyl derivative was a pasty mass with $[\alpha]_D^{16°}$ + 87·5° (*c* 2·0, chloroform); six recrystallisations from methyl alcohol yielded long needles of a second *benzoylcarvotanacetylamine*, with m. p. 165°, $[\alpha]_D$ — 87·5° (*c* 2·0, chloroform) (Found : C, 79·5; H, 8·7. $C_{17}H_{23}ON$ requires C, 79·3; H, 9·0%). The same derivative was obtained similarly from crude *d*-carvotanacetylamine having $\alpha_D^{14°}$ + 118·60° (*l* 1, homogeneous), prepared from *d*-carvotanacetone oxime as in (1) above.

Catalytic Hydrogenation of d-*Carvotanacetylamine Hydrogen* d-*Tartrate*.—A solution of this salt (6 g.) in methyl alcohol (150 c.c.) was hydrogenated in presence of a 2% palladised calcium carbonate catalyst (10 g.) for 45 minutes at a pressure of 3 atms. The residual salt had m. p. 150—160°, $[\alpha]_D^{17°}$ + 2·0° (*c* 2·0, water). Four recrystallisations from water containing a little methyl alcohol yielded a substance with m. p. 177—178°, $[\alpha]_D^{17°}$ + 6·0° (*c* 2·0, water). Admixture

of this substance with authentic *l-iso*carvomenthylamine hydrogen *d*-tartrate (J., 1935, 1143) did not affect the melting point. No other pure substance could be isolated from the mother-liquors.

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