193. *Reactions of αβ-Unsaturated Cyclic Aldehydes and Ketones. Part VI.* (+)-cis- *and* (−)-trans-*Cryptol from* (−)-*Cryptone.*

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Reduction of (−)-cryptone from the oil of *Eucalyptus cneorifolia* by means of aluminium *iso*propoxide gives a mixture consisting of 65% (−)-*trans*-cryptol with 35% of the hitherto unknown (+)-cis-*cryptol.* The separation, purification, and characterisation of the two epimers is described. The alcohols are of interest on account of the unusually high optical rotation and the excellent crystallising power of their derivatives.

The structure of (−)-cryptone [(−)-4-*iso*propyl*cyclo*hex-2-enone] permits the formation of two epimeric alcohols on reduction by aluminium *iso*propoxide. Galloway, Dewar, and Read (*J.*, 1936, 1595) described a lævorotatory alcohol from this source, and inferred the presence of a second, dextrorotatory form which was not isolated; later Macbeth and Winzor (*J.*, 1939, 264) prepared the enantiomer of the first product above, by reducing (+)-cryptone from water-fennel oil, and proved that their alcohol, and that of Galloway, Dewar, and Read, had the *trans*-configuration. Subsequently, Gillespie and Macbeth (*J.*, 1939, 1531) succeeding in preparing two epimeric DL-cryptols from DL-cryptone, and assigning configurations to each. But hitherto the optically active *cis*-epimers have not been described.

Cooke, Gillespie, and Macbeth (*J.*, 1939, 518) gave a ratio of 95% *trans* to 5% *cis*, but the indirect method of analysis used apparently was unreliable as the investigation of the product of large-scale reductions of (−)-cryptone has now shown that it is a mixture of about 65% (−)-*trans*-cryptol and 35% (+)-cis-*cryptol*, and that there are practically no by-products. The ratio of *trans* to *cis* does not vary much with different proportions of *iso*propoxide to ketone. The proportions present can be calculated from the optical rotation of the crude mixture and derived *p*-nitrobenzoate, and are confirmed by the quantities of epimers actually separated.

In the first instance the *cis*-epimer was separated by means of the allophanates formed on passing cyanic acid into the homogeneous alcohols. The precipitated allophanates were treated with cold chloroform, in which the *trans*-derivative is practically insoluble, and the *cis*-allophanate recovered from the extract was repeatedly recrystallised. Although the method allowed useful exploratory work to be done on the derivatives of the *cis*-alcohol it was later abandoned, as the yield of the *cis*-compound was not good and the purity was questionable.

The separation was ultimately effected by converting the crude cryptols into the *p*-nitrobenzoates. Simple recrystallisation gave a remarkably easy resolution into practically pure *trans*-*p*-nitrobenzoate, and another product containing 80% of *cis*-*p*-nitrobenzoate, which appeared as well-defined mixed crystals not resolved further by recrystallisation. Solubility relationships for the 3 : 5-dinitrobenzoates were more favourable, and permitted the final purification of the *cis*-cryptol. Some mixed crystal formation also seemed to take place with the epimeric 3 : 5-dinitrobenzoates, and likewise the allophanates could not be separated completely by crystallisation although the *cis*-allophanate was far more soluble than the *trans*.

The epimeric cryptols are now readily available and should provide interesting material for optical studies. The high rotations characteristic of the series are illustrated in the table in which all values were determined using 0·1M-solutions. For the esters, but not for the free alcohols, the rotations of the *cis*- and *trans*- forms are nearly equal but of opposite sign, resembling optical antipodes rather than geometrical isomers derived from the same ketone. A more complex but apparently analogous situation in the menthol series has been discussed by Read (*Chem. Reviews*, **1930**, **7**, 1).

Rotations of Cryptol Derivatives at 21°.

(All solutions M/10, and in chloroform unless specified.)

Derivative.	$[\alpha]_D$, *trans.*	$[\alpha]_D$, *cis.*	$[M]_D$, *trans.*	$[M]_D$, *cis.*
p-Nitrobenzoate	−171°	+187°	−49,400°	+54,000°
3 : 5-Dinitrobenzoate	−150	+155	−50,000	+51,800
Hydrogen phthalate	−140	+144	−40,300	+41,500
Phenylurethane	−150	+150	−38,900	+38,900
α-Naphthylurethane	−132	+134	−40,800	+41,400
Allophanate (in chloroform)	insol.	+172	—	+39,000
Allophanate (in dioxan)	−136	+141	−30,700	+31,800
Free alcohols (in chloroform)	−118	+ 74	−16,500	+10,400

(−)-Cryptone (in chloroform) $[\alpha]_D$ −90°, $[M]_D$ −12,400°.
(−)-Cryptone oxime $[\alpha]_D$ −106·4°, $[M]_D$ −16,300°.

The *cis*-configuration assigned to the new epimer was confirmed by its having a higher density and refractive index, and giving lower-melting derivatives, and by the direct reduction of its hydrogen phthalate to *cis*-dihydrocryptol hydrogen phthalate. cis-*Cryptol hydrogen phthalate* was saponified less readily than the *trans*-hydrogen phthalate, but the difference in the rates of saponification was not as great as for the dihydrocryptol hydrogen phthalates (Cooke, Gillespie, and Macbeth, *loc. cit.*).

Optically pure (−)-cryptone was prepared from the pure cryptols in several ways, and a freshly purified specimen with $\alpha_D^{20\cdot5^\circ}$ − 65·9° (homogeneous), $[\alpha]_D^{20^\circ}$ − 91·7° (*c* 2·2 in alcohol), was obtained, which is probably near the maximum attainable rotation. It was impossible to duplicate the high value of $[\alpha]_D$ − 119·3° (*c* 2·0 in alcohol) reported by Galloway, Dewar, and Read (*loc. cit.*), and indeed we have never attained this value in these laboratories with either D- or L-cryptone. Evidently the cryptone in the oil of *E. cneorifolia* is practically optically pure, and does not suffer much racemisation during long keeping or on treating its bisulphite compound with concentrated alkali during the isolation of the ketone. Its oxime, previously reported as a liquid (Berry, Macbeth, and Swanson, *J.*, **1937**, 987), was obtained as a solid.

EXPERIMENTAL.

Ponndorf Reduction.—Various samples of crude cryptone up to 8 years old were combined and purified through the bisulphite compound (Berry, Macbeth, and Swanson, *loc. cit.*) and redistilled; b. p. 60°/1 mm., α_D − 64° (homogeneous), $[\alpha]_D$ − 93° (*c* 2·1 in alcohol). Cryptone (92·5 g.) was dissolved in a 0·5M-solution (600 ml., 1·35 equivs.) of distilled aluminium *iso*propoxide in *iso*propyl alcohol, and submitted to 5 hours of slow constant-volume distillation, until the acetone test was negative; reaction was substantially finished in 3 hours. The *iso*propyl alcohol was removed, the residue hydrolysed by ice and 10N-sulphuric acid, and the cryptols extracted and distilled, forming a viscous colourless oil, b. p. 62°/0·3 mm., $\alpha_D^{20^\circ}$ − 46·2° (homogeneous); yield, 94% with little residue.

In subsequent runs the volume of 0·5M-*iso*propoxide solution was varied to give different ratios of *iso*propoxide to cryptone, and with 1·13 equivs. of *iso*propoxide, yield was 91%, $\alpha_D^{20^\circ}$ − 46·8°; with 1·14 equivs., 93%, − 47·8°; with 2·0 equivs., 96%, − 48·2°. The higher ratios gave a faster reaction, and the non-volatile residue was very small.

(−)-trans-*Cryptol.*—The cryptols (72 g.) mixed with pyridine (60 ml.) in dry benzene (100 ml.) were stirred and treated gradually with *p*-nitrobenzoyl chloride (99 g.) in benzene 250 ml.) during 15 minutes at 10—20°. The mixture was held at 20° for 2 hours then refluxed for 1 hour. Removal of pyridine hydrochloride and a little *p*-nitrobenzoic acid, and steam-distillation of benzene and traces of cryptol, left the crude *p*-nitrobenzoate as a waxy yellow solid, melting range 36—65°, $[\alpha]_D^{20^\circ}$ − 34·3° (*c* 2·0 in chloroform); yield, 99%. To ensure a satisfactory separation of the *cis*-epimer, the crude solid was given a preliminary treatment by dissolving it in hot methyl alcohol (1·5—2·0 ml./g.) and slowly cooling to 5°; recovery, 80—85% of pale yellow granules, melting range 37—70°, $[\alpha]_D$ − 51°. This material was divided into 6 parts and recrystallised systematically from methyl alcohol (initially 3 ml./g., later 6 ml./g.), cooling not below 18°. After crystallisation of the head fraction 4 and the tail 10 times, 56% was recovered with m. p. over 80°, and a recrystallisation gave pure (−)-*trans*-cryptol *p*-nitrobenzoate, m. p. 83·4°. Hydrolysis by refluxing for 40 minutes with 4% methyl-alcoholic potassium hydroxide (1·25 mols.) gave (−)-*trans*-cryptol in 93% yield, b. p. 60°/0·5 mm., $\alpha_D^{20^\circ}$ − 136·8° (homogeneous), $d_4^{30^\circ}$ 0·9261, $n_D^{20^\circ}$ 1·4793.

(+)-cis-*Cryptol.*—The mother liquors from all stages except the last in the fractional crystallisation of the mixed *p*-nitrobenzoates were cooled to 5°, and quickly deposited pale yellow granules, m. p. 35—39°, $[\alpha]_D$ + 104° approximately (chloroform), amounting to 37·5% of the starting material. Recrystallisation from methyl alcohol caused no change in m. p. or rotation. Hydrolysis yielded (96%) an alcohol with $\alpha_D^{22°}$ + 41·2° (homogeneous), corresponding to a mixture of 78% of (+)-*cis*- and 22% of (−)-*trans*-cryptol. This very ready separation of the *p*-nitrobenzoates was confirmed for a mixture of the pure *p*-nitrobenzoates. On dissolving (−)-*trans*-cryptol *p*-nitrobenzoate (4·4 g.) and (+)-cis-*cryptol* p-*nitrobenzoate* (3·7 g.) in methyl alcohol (40 ml.) and cooling to 18°, the solution deposited solid with $[\alpha]_D^{23°}$ − 100° (chloroform) (4·7 g.), then on cooling the mother liquors to 5°, material with $[\alpha]_D^{23°}$ + 109° was obtained (2·0 g.).

The cryptol mixture with $\alpha_D^{22°}$ + 41° was converted into the 3 : 5-dinitrobenzoate by the method described for the *p*-nitrobenzoate, but with 60% more benzene. A practically quantitative yield was obtained, melting range 80—105°, $[\alpha]_D^{20°}$ + 95° (*c* 2·0 in chloroform). Systematic fractional crystallisation in three batches was carried out from methyl alcohol (12 ml./g., later 20 ml./g.), and 6 crystallisations at 20° gave a 38% recovery of material m. p. > 111°. A final recrystallisation from light petroleum (b. p. 90—140°, 6 ml./g.) gave pure (+)-cis-*cryptol* 3 : 5-*dinitrobenzoate* as fine brittle needles, m. p. 112·5—113·5°, $[\alpha]_D^{21°}$ + 155° (*c* 3·3 in chloroform) (Found : C, 57·5; H, 5·5. $C_{16}H_{18}O_6N_2$ requires C, 57·5; H, 5·4%). It is probable that light petroleum would be better than methyl alcohol for the fractional crystallisation.

Hydrolysis of the pure 3 : 5-dinitrobenzoate by boiling it for 20 minutes with 2·5% methyl-alcoholic potassium hydroxide (1·2 mols.) gave a 96% yield of (+)-cis-*cryptol*, a viscous oil with the same strong fragrant odour as the *trans*-epimer, b. p. 70°/1·5 mm., $\alpha_D^{14\cdot5°}$ + 90·2° (homogeneous), $d_{4°}^{20°}$ 0·9293, $n_D^{20°}$ 1·4811.

The methyl alcohol mother liquors from the systematic crystallisation were concentrated, yielding a solid with $[\alpha]_D$ − 47° approx., m. p. 90° (fairly sharp); these properties did not change appreciably in two recrystallisations from methyl alcohol.

Derivatives of Cryptols (rotations in table).—Both cryptols were dehydrated by phthalic anhydride alone at 110°, but could be esterified in excellent yield in pyridine solution at 50—60°. The esters were recrystallised from light petroleum (b. p. 60—90°) ; (−)-trans-*cryptol hydrogen phthalate* formed colourless thin leaves, m. p. 85—86° (Found : C, 70·8; H, 6·9. $C_{17}H_{20}O_4$ requires C, 70·8; H, 6·9%); (+)-cis-*cryptol hydrogen phthalate* formed large clear prisms, m. p. 68·5—70° (Found : C, 70·9; H, 6·65%). On mixing equivalent quantities of the hydrogen phthalates and piperazine in acetone, the respective *piperazine* salts were obtained; the *trans* formed small shining plates, m. p. 154—156° (decomp.) (Found : N, 4·15. $C_{38}H_{50}O_8N_2$ requires N, 4·25%); the *cis* formed small needles, m. p. 150—151° (decomp.) (Found : N, 4·1%).

The phenylurethanes and α-naphthylurethanes, made by standard methods, were recrystallised from light petroleum (b. p. 40—60° and 60—90°, respectively); the (−)-trans-*phenylurethane* formed silky needles, m. p. 106—107° (Found : C, 74·4; H, 8·1; N, 5·4. $C_{16}H_{21}O_2N$ requires C, 74·1; H, 8·2; N, 5·4%); the (+)-cis-*phenylurethane* formed very soluble pearly flakes, m. p. 56·5—57·5° (Found : C, 74·1; H, 8·15%); the (−)-trans-α-*naphthylurethane* formed fine white needles, m. p. 118·5—119·5° (Found : C, 77·8; H, 7·3; N, 4·5. $C_{20}H_{23}O_2N$ requires C, 77·6; H, 7·5; N, 4·5%); the (+)-cis-α-*naphthylurethane* was a felt-like mass, m. p. 98—99° (Found C, 77·5; H, 7·4%).

(+)-cis-*Cryptol* p-*nitrobenzoate*, prepared from the pure alcohol, separated from methyl alcohol in glistening scales, m. p. 48·5—49·5° (Found : N, 4·65. $C_{16}H_{19}O_4N$ requires N, 4·85%).

For (−)-*trans*-cryptol 3 : 5-dinitrobenzoate the rotation and melting point were greater than the figures given by Galloway, Dewar, and Read (*loc. cit.*); slender needles from methyl alcohol, m. p. 120—121° (Found : N, 8·65. Calc. for $C_{16}H_{18}O_6N_2$: N, 8·4%).

The cryptols did not react with cyanic acid in ether, benzene, or chloroform solution, but on passing cyanic acid gas into the homogeneous alcohols, conveniently absorbed in glass wool, fair yields of *allophanates* were obtained; the *trans*- formed long needles from chlorobenzene, m. p. 196—197° (efferv.) (Found : C, 58·5; H, 8·1; N, 12·3. $C_{11}H_{18}O_3N_2$ requires C, 58·35; H, 8·0; N, 12·2%); the *cis*- formed minute needles from toluene, m. p. 166—168° (Found : N, 12·5%). From the more soluble portions of the *cis*-allophanate a small yield of (+)-cis-*cryptol urethane* was isolated as small needles from light petroleum, m. p. 118—119° (Found : C, 65·5; H, 9·3; N, 7·6. $C_{10}H_{17}O_2N$ requires C, 65·5; H, 9·35; N, 7·65%). The corresponding *trans*-urethane was not found. As the *trans*-allophanate was practically insoluble in cold chloroform, and the *cis*-allophanate readily soluble, an attempt was made to use these properties as a basis for separation; but the *cis*-cryptol could not be obtained pure in this way.

Oxidation to (−)-*Cryptone*.—Several lots of pure cryptols (4 to 8 g.) were oxidised, using three methods : (*a*) addition of cryptol to Beckmann chromic acid mixture at 55°, (*b*) liberation of chromic acid from potassium dichromate in presence of cryptol, by slow addition of sulphuric acid at 50—60°, (*c*) oxidation with chromium trioxide in acetone, under the conditions used by Bowden, Heilbron, Jones, and Weedon (*J.*, 1946, 39) for the oxidation of oct-3-yn-2-ol. Both *cis*- and *trans*-cryptol gave yields of 75—85% in all cases, $\alpha_D^{16°}$ − 64° to − 65°, but the products did not appear to be homogeneous. The products were mixed, and after conversion into the bisulphite compound and regeneration with alkali, a sample of (−)-cryptone was obtained with b. p. 48°/0·45 mm., $\alpha_D^{20\cdot5°}$ − 65·9° (homogeneous), $[\alpha]_D^{20°}$ − 91·7° (*c* 2·2 in alcohol), $d_{4°}^{20°}$ 0·9352, $n_D^{20°}$ 1·4830.

When (−)-cryptone was allowed to react with hydroxylamine hydrochloride in the presence of sodium carbonate, and the resulting oily oxime was distilled under reduced pressure, a semi-solid product was obtained. Three recrystallisations from light petroleum (b. p. 40—60° at 0°) gave the solid form of (−)-*cryptone oxime* as large plates, m. p. 56·5—57·5° (Found : N, 9·2. $C_9H_{15}ON$ requires N, 9·15%).

Configuration of (+)-cis-*Cryptol*.—(*a*) (+)-*cis*-Cryptol hydrogen phthalate dissolved in glacial acetic acid was shaken with hydrogen in the presence of platinum oxide until somewhat more than the theoretical amount of hydrogen had been absorbed. Dilution of the solution with water and recrystallisation of the product from light petroleum gave *cis*-dihydrocryptol hydrogen phthalate, m. p., and mixed m. p. with an authentic sample, 128—130°. (*b*) The rate of hydrolysis of (+)-*cis*- and

(—)-*trans*-cryptol hydrogen phthalates at 30° was followed in 0·1N-sodium hydroxide, and gave the values: $k^{30^\circ}_{trans}$ 9·08 × 10^{-4}; $k^{30^\circ}_{cis}$ 5·11 × 10^{-4} (mol., $l.^{-1}$, $sec.^{-1}$).

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