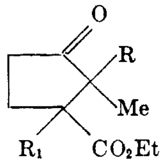
[CONTRIBUTION FROM THE INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE]

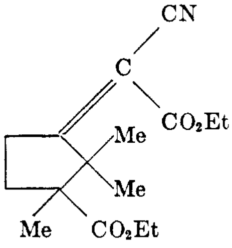
SYNTHETIC INVESTIGATIONS IN THE CAMPHOR SERIES. PART II. TOTAL SYNTHESIS OF *dl*-HOMOCAMPHORIC ACID[1]

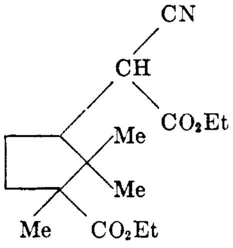
P. B. TALUKDAR AND P. BAGCHI

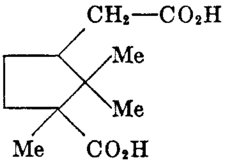
Received June 17, 1954

The classical Haller-Komppa (1, 2) synthesis of camphor involves reduction of camphoric anhydride by sodium amalgam to campholide. This procedure, however, does not unequivocally establish the structure of the latter, in as much as reduction of either of the two carbonyl groups may have taken place. From a purely synthetic point of view, therefore, the above synthesis of homocamphoric acid or camphor can not be regarded as unambiguous. This loophole can evidently be avoided by an independent unambiguous synthesis of homocamphoric acid. With this object in view the present work was initiated and has resulted in a total synthesis of *dl*-homocamphoric acid identical in all respects with the compound prepared from *dl*-comphor. Since *dl*-homocamphoric acid has already been converted to *dl*-camphor and *d*-camphor (2), our synthesis also constitutes a new unambiguous total synthesis of this natural product.


I


II


III


IV

In part I of this series, we have already described a new synthesis of ethyl camphononate (I, R = R_1 = Me). Model experiments on ethyl 2,2-dimethylcyclopentane-1-one-3-carboxylate (I, R = Me, R_1 = H) (to be described in Part III) indicated that a Knoevenagel synthesis with ethyl cyanoacetate should be preferred to a Reformatsky reaction with ethyl bromoacetate for the introduction of an acetic acid side chain. Accordingly, ethyl camphononate (I, R = R_1 = Me) was condensed with ethyl cyanoacetate, but unfortunately the yield of the cyclopentylidenecyanoacetate (II) was unsatisfactory following either the original method of Cope, *et al.* (3) or the lot addition technique of Cragoe, *et al.* (4). Persistant attempts to effect improvement in the yield of II by altering the proportion of the catalyst (ammonium acetate) and varying experimental conditions were uniformly unsuccessful. A Reformatsky reaction was also attempted with even less encouraging results. This observation was rather unexpected [*cf.* however, Lapworth and Chapman (5)] in view of our experience with ethyl 2,2-dimethylcyclopentane-1-one-3-carboxylate (I, R = Me, R_1 = H; *cf.* Part

---

[1] A preliminary communication appeared in *Science and Culture* (*India*) **19**, 416 (1954).

III). The ester II, however, showed the characteristic absorption band at 238.5 mμ (log E 4.07) expected for an alkylidenecyanoacetate (6).

Reduction of the cyclopentylidenecyanoacetate (II) was carried out over palladized charcoal (5%) and the resultant saturated cyano ester (III) underwent smooth hydrolysis with hydrochloric acid giving the acid IV which, after two crystallizations melted at 232°; Komppa (2) recorded m.p. 231–232° for his synthetic *dl*-homocamphoric acid. The mixture m.p. with authentic *dl*-homocamphoric acid (7) was undepressed.

Isolation of a single isomer of IV in the final step indicates that catalytic reduction of the ester II proceeds stereospecifically. The product IV is assigned the *cis*-structure on the basis of observations of Linstead, *et al.* (8) and Conroy (9), a contention substantiated by the identity of the synthetic product with natural *dl*-homocamphoric acid.

Our thanks are due to Dr. P. C. Dutta for his kind interest and helpful suggestions.

EXPERIMENTAL[2]

Ethyl 2,2,3-trimethyl-3-carbethoxycyclopentylidenecyanoacetate (II). A mixture of ethyl camphononate (I, R = R_1 = Me; 15 g.), ethyl cyanoacetate (17 g.), glacial acetic acid (7.2 g.), dry benzene (30 ml.), and ammonium acetate (4.7 g.) was gently refluxed until separation of water was complete. Then another lot of ammonium acetate (0.5 g.) was added and refluxing was continued until separation of water was complete. The process was repeated twice more and finally cooled and thoroughly washed with water. Removal of benzene gave an oil which after distillation gave 3.9 g. of a light yellow substance, b.p. 170°/2 mm with a forerun of a mixture of ethyl camphononate and ethyl cyanoacetate.

Anal. Calc'd for $C_{16}H_{23}NO_4$: C, 65.56; H, 7.85.

Found: C, 65.10; H, 8.21.

Ultraviolet absorption: λ_{max}^{alc} 238.5 mμ; log E 4.07.

Ethyl 2,2,3-trimethyl-3-carbethoxycyclopentylcyanoacetate (III). A solution of the unsaturated cyanoester II (3.80 g.) in absolute alcohol (25 ml.) was stirred with pre-reduced palladized charcoal (5%, 0.30 g.) in an atmosphere of hydrogen. Rapid absorption of hydrogen took place and it was allowed to proceed until a little over the theoretical volume of hydrogen (503 ml., required 489 ml.) was absorbed. The solution was filtered, and the residual oil after removal of alcohol was taken up in ether. The ether extract was washed with water, dilute hydrochloric acid, water, dilute sodium bicarbonate solution, and water. The extract was dried over sodium sulfate and finally distilled giving 2.30 g. of colorless oil, b.p. 170–173°/5 mm.

Anal. Calc'd for $C_{16}H_{25}NO_4$: C, 65.08; H, 8.48.

Found: C, 65.56; H, 8.83.

dl-Homocamphoric acid (IV). A mixture of the above ester III (1.60 g.) and hydrochloric acid (20 ml.) was refluxed for 30 hours in an oil-bath at 120–130°. The crude acid was collected by filtration, crystallized once from hot water, and then sublimed. The material thus obtained after two crystallizations from hot water containing a few drops of hydrochloric acid melted sharply at 232°. The literature (2) gives for *dl*-homocamphoric acid, m.p. 231–232° synthesized from camphoric anhydride.

Anal. Calc'd for $C_{11}H_{18}O_4$: C, 61.68; H, 8.40.

Found: C, 61.77; H, 8.43.

Preparation of dl-homocamphoric acid from dl-camphor. Hydroxymethylene camphor was prepared from *dl*-camphor and this on treatment with hydroxylamine hydrochloride

---

[2] All melting points are uncorrected.

and aqueous caustic soda furnished cyanocamphor (7). Crude cyanocamphor on further hydrolysis with aqueous alkali gave an acid which, after two crystallizations from water followed by sublimation in a high vacuum and crystallization from water, gave white crystals melting at 231–232°. The mixture m.p. with synthetic acid IV was undepressed.

SUMMARY

Condensation of ethyl *dl*-camphononate with ethyl cyanoacetate followed by catalytic reduction and hydrolysis gave *dl*-homocamphoric acid identical with the acid prepared from *dl*-camphor.

JADAVPUR, CALCUTTA—32

REFERENCES

(1) HALLER, *Compt. rend.*, **122**, 446 (1896); **109**, 68, 112 (1889); HALLER AND BLANC, *Compt. rend.*, **130**, 376 (1900).

(2) KOMPPA, *Ber.*, **41**, 4470 (1908); *Ber.*, **36**, 4332 (1903); KOMPPA, *Ann.*, **370**, 209 (1909).

(3) COPE, HOFMAN, WYCKOFF, AND HARDENBERGH, *J. Am. Chem. Soc.*, **63**, 3452 (1941).

(4) CRAGOE, ROBB, AND SPRAGUE, *J. Org. Chem.*, **15**, 381 (1950).

(5) LAPWORTH AND CHAPMAN, *J. Chem. Soc.*, **77**, 446 (1900).

(6) BAGCHI, BERGMANN, AND BANERJEE, *J. Am. Chem. Soc.*, **71**, 989 (1949).

(7) LAPWORTH, *J. Chem. Soc.*, **77**, 1053 (1900).

(8) LINSTEAD, DOERING, DAVIS, LEVINE, AND WHETSTONE, *J. Am. Chem. Soc.*, **64**, 1985 (1942).

(9) CONROY, *J. Am. Chem. Soc.*, **74**, 3046 (1952).