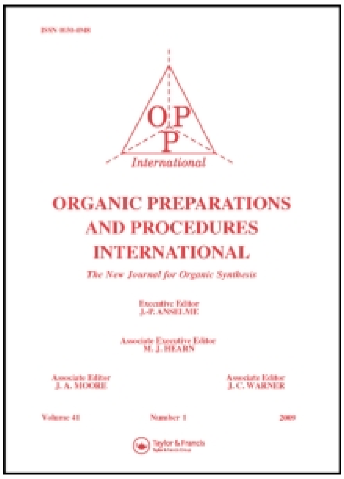

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BENZOCYCLOHEPTENE DERIVATIVES FROM THE HOESCH REACTION

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BENZOCYCLOHEPTENE DERIVATIVES FROM THE HOESCH REACTION

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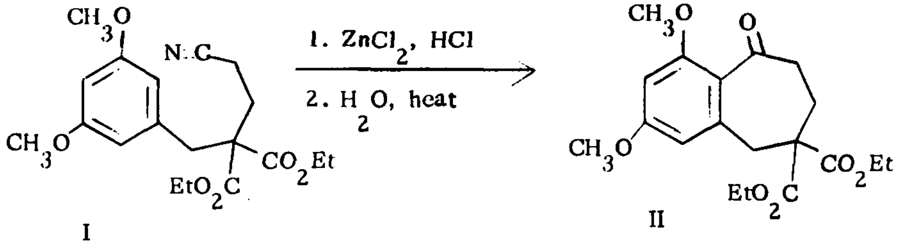
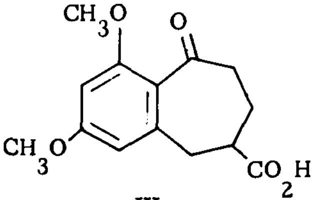
In the course of an ongoing study, a route for the preparation of a benzocycloheptene derivative (III), bearing strategically placed, synthetically useful substituents on the 7-membered ring, was required. It was speculated that a nitrile system such as I might be amenable to cyclization to II under conditions of the Hoesch reaction.[1,2]



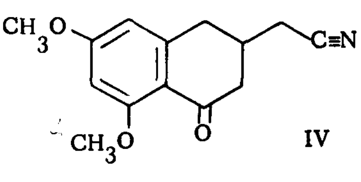
I

II

Although the literature revealed little precedent for intramolecular Hoesch reactions, we have found that I can be cyclized to II in good yield under classic Hoesch reaction conditions. Subsequent to completion of the work described herein, Hatch et al.[3] reported a Hoesch cyclization to the α-tetralone IV, in 93% yield.



III



IV

The Hoesch reaction may be of general utility in cyclization to 6- and 7-membered carbocyclic ring systems. The Hoesch cyclization described here provides a direct, simple route to a benzocycloheptene which presents many possibilities for further elaboration of the molecule. Moreover, the hydrolysis of the imine precursor to II under neutral conditions provides the possibility of inclusion of acid labile groups in the molecule.

EXPERIMENTAL

Melting points were determined in open glass capillaries and are uncorrected. Nmr spectra were recorded on a Varian Associates T-60 instrument, using tetramethylsilane as the internal standard. IR spectra were recorded with a Perkin Elmer 267 instrument. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

4,4-Dicarbethoxy-5-(3,5-dimethoxyphenyl)-pentanenitrile (I). - A 50% mineral oil dispersion of NaH (4.66 g, 0.0972 mol), under a stream of N_2, was washed three times with pentane, then 100 mL of Na-dried benzene was added. To the resulting slurry and in a stream of N_2 was added dropwise 19.57 g (0.0917 mol) of diethyl 2-(2-cyanoethyl) malonate (Aldrich) in 50 mL of dry benzene. The resulting mixture was stirred overnight at room temperature, then was heated under reflux for 2 h. To the refluxing mixture was then added dropwise 20.59 g (0.0891 mol) of 3,5-dimethoxybenzyl bromide[4] in 100 mL of dry benzene, and this mixture was heated under reflux overnight. The cooled reaction mixture was washed with H_2O until the washings were neutral to pH paper. The organic layer was dried ($MgSO_4$), filtered, and volatiles were removed under reduced pressure, to afford a pale yellow oil which solidified upon standing at room temperature. This material was recrystallized from benzene-petroleum ether to give 24.5 g (76%) of white plates, mp 82.5-83.5^{o}. IR ($CHCl_3$): 2250, 1725, 1595 cm^{-1}; NMR ($CDCl_3$): δ 1.30 (t, 6 H,

OCH_2CH_3), 2.25 (m, 4 H, $CH_2CH_2C{\equiv}N$), 3.17 (s, 2 H, CH_2), 3.71 (s, 6 H, OCH_3), 4.20 (q, 4 H, OCH_2CH_3), 6.15 (d, 2 H, J = 2 Hz, 2,6-Arom H), 6.28 (d, 1 H, J = 2 Hz, 4-Arom H).

Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.79 ; H, 6.93 ; N, 3.85. Found: C, 62.66 ; H, 7.09 ; N, 3.76 .

6,6-Dicarbethoxy-1,3-dimethoxy-9-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene (II). - Anhydrous HCl was bubbled through a stirred slurry of 10 g of purified Zn dust in 150 mL of anhydrous ether under a slight positive N_2 pressure. After several hours, evolution of H_2 ceased and a thick, colorless oil separated at the bottom of the reaction vessel. The nitrile I (10 g, 0.0275 mol) was added in one portion, and stirring was continued at room temperature for 20 h. The ether was removed in a stream of N_2 and 10% $NaHCO_3$ was slowly added with stirring, to bring the mixture to pH 7. The mixture was then heated on a steam bath for 20 min., cooled, and extracted several times with ether. The pooled ethereal extracts were washed with H_2O, dried ($MgSO_4$), filtered, and the filtrate was evaporated under reduced pressure to leave a pale yellow oil which crystallized upon standing at room temperature. This material was recrystallized from ether-pentane (10:1) to give 6.8 g (66%) of white crystals, mp 94-95.5°. IR ($CHCl_3$): 1725, 1675, 1600 cm^{-1}; NMR ($CDCl_3$): δ 1.30 (t, 6 H, OCH_2CH_3), 2.23 (m, 2 H, $COCH_2CH_2$), 2.63 (m, 2 H, $COCH_2CH_2$), 3.22 (s, 2 H, CH_2), 3.79 (s, 6 H, OCH_3), 4.20 (q, 4 H, OCH_2CH_3), 6.25 (d, 1 H, J = 2 Hz, Arom H), 6.37 (d, 1 H, J = 2 Hz, Arom H).

Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.63 ; H, 6.64. Found: C, 62.80 ; H, 6.86 .

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REFERENCES

1. P. E. Spoerri and A. S. Du Bois, Org. React., 5, 387 (1949).
2. W. Ruske in "Friedel-Crafts and Related Reactions," Vol. III, Part 1, G. A. Olah, Ed., Interscience Publishers, New York, N. Y., 1964, Chapter XXXII.
3. R. P. Hatch, J. Shringarpure, and S. M. Weinreb, J. Org. Chem., 43, 4172 (1978).
4. A. Bhati, Tetrahedron, 18, 1519 (1962).

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