[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ISRAEL INSTITUTE OF TECHNOLOGY]

Colchicine Studies. III. Conversion of 2-(2′,3′,4′-Trimethoxyphenyl)-cyclohept-2-enone to a Tropone[1a]

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The synthesis of 2-(5′-bromo-2′,3′,4′-trimethoxyphenyl)tropone from 2-(2′,3′,4′-trimethoxyphenyl)cyclohept-2-enone is described.

In order to test the feasibility of aromatization of a substituted cyclohept-2-enone through bromination-dehydrobromination, as a model for a more complex tricyclic intermediate, the reaction of 2-(2′,3′,4′-trimethoxyphenyl)cyclohept-2-enone with *N*-bromosuccinimide (NBS) was studied.

The synthesis of this ketone has been reported previously,[2–4] but an improved procedure has now been developed. Treatment of 2′,3′,4′-trimethoxyphenylcycloheptene with crystalline nitrosylsulfuric acid,[5] followed by appropriate work-up gave the oxime of the desired ketone in higher yield than previously obtained and in higher degree of purity. The ketone resulting from acid hydrolysis of the oxime was a low-melting solid which was also purer than has been hitherto obtained.

Although it was possible to obtain 2-phenyltropone from 2-phenyl-cyclohept-2-enone by stepwise bromination-dehydrobromination,[6] this method was not practicable in the present case. Several competing brominations occur and, as expected, the aromatic nucleus is attacked by NBS as well as the alicyclic ring.[7]

Since stepwise reaction yielded intractable mixtures, it was hoped that bromination of the α,β-unsaturated ketone with three moles of NBS (one to satisfy the aromatic nucleus, two for the alicyclic ring) would be followed by spontaneous dehydrobromination, the driving force being the aromatization of the alicyclic ring. Although hydrogen bromide was indeed evolved during the bromination it complicated the reaction through partial addition to the products. The reaction mixture was refluxed with collidine and after work-up and chromatography, it was possible to characterize one of the chromatographic fractions as a tropone. Clearly, from the viewpoint of yield, this method is unsatisfactory.

The product, 2-(5′-bromo-2′,3′,4′-trimethoxyphenyl)tropone gives a 2,4-dinitrophenylhydrazone in contradistinction to tropone itself.[8] The tropone derivative took up four moles of hydrogen and yielded 2-(2′,3′,4′-trimethoxyphenyl)cycloheptanone.[4,9] That the bromine atom in the benzene ring is in the indicated position seems most probable in view of the behavior of pyrogallol trimethyl ether on bromination.[10]

EXPERIMENTAL[11]

1-(2′,3′,4′-Trimethoxyphenyl)cycloheptene was prepared as previously described.[2]

2-(2′,3′,4′-Trimethoxyphenyl)cyclohept-2-enone oxime. Powdered sodium nitrite (2.4 g). was added slowly to concentrated sulfuric acid (20 ml.) with stirring and cooling (ice-salt), maintaining the temperature below 5°. The mixture was then warmed to 60° until a clear solution was obtained.

It was then cooled to −5° and 1-(2′,3′,4′-trimethoxyphenyl)cycloheptene (8.8 g.) was added dropwise with stirring. The temperature of the strongly exothermic reaction was maintained between −5° and 0° during the addition. Stirring was continued for an additional 30 min. and the mixture was poured on ice. The brownish precipitate (7 g.) was removed by filtration and was refluxed for 15 min. with 10% aqueous potassium carbonate solution (50 ml.). After cooling, the mixture was extracted with ether, the ether extract was shaken with Claisen alkali, the alkaline layer was acidified, re-extracted with ether and the ether solution was dried (sodium sulfate) and the solvent removed by distillation. Trituration of the crude product thus obtained with cold ethanol yielded colorless *oxime* (3 g.; 35% yield), m.p. 95°. Crystallization from methylcyclohexane afforded the analytical sample of double melting point, 94–95° and 109°. (Fisher Johns block).

Anal. Calcd. for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.27; N, 4.81. Found: C, 66.10; H, 7.32; N, 4.86.

2-(2′,3′,4′-Trimethoxyphenyl)cyclohept-2-enone. The above oxime (5 g.) was heated under reflux with concentrated hydrochloric acid (5 ml.) and water (30 ml.). The cooled mixture was then extracted with benzene and the benzene extract was washed with 10% aqueous potassium carbonate and with water and dried over sodium sulfate. Removal of the solvent yielded tarry material (4.5 g.). Distillation yielded the *ketone* (3.6 g.), b.p. 150–160° (0.2 mm.). It solidified on cooling, m.p. 53° (from methylcyclohexane).

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(1) (a) Presented at XIXth meeting of Israel Chemical Association, Rehovot, June, 1956. (b). In partial fulfillment of the requirements for the D.Sc. degree, Israel Institute of Technology, September, 1955.

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(11) All melting and boiling points are uncorrected.

Infrared absorption: 5.99 μ (C=O). Lit.[3,4] reports the ketone as an oil.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30; OCH_3, 33.66. Found: C, 69.28; H, 7.47; OCH_3, 33.76.

The *semicarbazone* formed colorless needles, m.p. 182–183° (dec.) (from methylcyclohexane). Lit.[4] reports 183–184° dec.

Anal. Calcd. for $C_{17}H_{23}N_3O_4$: C, 61.24; H, 6.95; N, 12.61. Found: C, 61.31; H, 6.88; N, 12.51.

The *2,4-dinitrophenylhydrazone* formed orange needles, m.p. 170° (dec.) (from nitromethane). This is β-form which can also be obtained by long refluxing of α-form, m.p. 121–123° with acid.[3]

Anal. Calcd. for $C_{22}H_{24}N_4O_7$: C, 57.89; H, 5.30; N, 12.28. Found: C, 57.93; H, 5.13; N, 12.64.

2-(2',3',4'-Trimethoxyphenyl)cycloheptanone. The unsaturated ketone (1.3 g.) in ethanol (50 ml.) was reduced in the presence of 10% palladium-charcoal at room temperature and atmospheric pressure. One mole of hydrogen was absorbed during 20 min. Removal of the catalyst and solvent afforded the saturated *ketone* (1.3 g). as a pale yellow oil, b.p. 160° (0.2 mm.). It was characterized as the *semicarbazone*, colorless plates, m.p. 148° (dec.) (from ethanol).

Anal. Calcd. for $C_{17}H_{25}N_3O_4$: C, 60.88; H, 7.51; N, 12.53. Found: C, 60.72; H, 7.49; N, 12.51.

The *2,4-dinitrophenylhydrazone* formed orange crystals, m.p. 152° (from ethanol–ethyl acetate). Lit.[4,9] reports m.p. 153–154°.

2-(5'-Bromo-2',3',4'-trimethoxyphenyl)tropone. 2-(2',3',4'-trimethoxyphenyl)cyclohept-2-enone (3 g.), *N*-bromosuccinimide (5.8 g.), and a catalytic amount of dibenzoyl peroxide were heated under reflux in carbon tetrachloride (50 ml.). The reaction was over after 3 hr. and some spontaneous dehydrobromination was observed. The succinimide was removed by filtration and the solvent was removed *in vacuo* (water pump). Collidine (20 ml.) was added to the residue and the mixture was heated under reflux for 4 hr. After cooling, the precipitated collidine hydrobromide was removed by filtration, the collidine remaining was removed *in vacuo*, and the residue was taken up in benzene. The bezene extract was washed with dilute hydrochloric acid, with water, dried over sodium sulfate, and the solvent was removed.

A benzene solution of the residue was chromatographed over acid-washed alumina (Merck), using benzene and finally benzene-chloroform (4:1) for elution. Five distinct bands could be observed on the column and these fractions were worked up separately. Infrared spectra and analyses showed that these were apparently bromo-enones and bromodienones but it was not possible to purify these sufficiently for characterization. Fortunately, however, one of these fractions turned out to be the *bromotropone* derivative. The compound was an oil (300 mg.), distilled at bath temp. 190° (0.05 mm.). Infrared absorption (cm.$^{-1}$): 1700 (m), 1675 (m), 1625 (s), 1585 (s), 1488 (vs), 1305 (m), 1270 (m), 1228 (w), 1100 (vs), 1065 (m).

Anal. Calcd. for $C_{16}H_{15}O_4Br$: C, 54.70; H, 4.27; Br, 22.79; OCH_3, 26.50. Found: C, 54.66; H, 4.21; Br, 22.20; OCH_3, 25.80.

The *2,4-dinitrophenylhydrazone* formed deep red clusters of needles, m.p. 132–134° (from ethanol–ethyl acetate).

Anal. Calcd. for $C_{22}H_{19}BrN_4O_7$: C, 49.72; H, 3.58; N, 10.54. Found: C, 49.42; H, 3.26; N, 10.18.

Hydrogenation of the bromotropone. The bromotropone (60 mg.) was reduced in ethanol with 10% palladium-charcoal at room temperature and atmospheric pressure. Four moles of hydrogen were absorbed during 6 hr. and working up yielded a *2,4-dinitrophenylhydrazone*, melting point and mixed melting point with an authentic specimen of the corresponding derivative of 2-(2',3',4'-trimethoxyphenyl)cycloheptanone, 152°.

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Mescaline Analogs. VIII. Substituted 5-Methoxy- and 5,6,7-Trimethoxyindoles

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Several 5-methoxy- and 5,6,7-trimethoxyindole derivatives have been synthesized by the cyclization of appropriately substituted open chain amines. Convenient syntheses of 1-benzyl-3-hydroxy-3-carboethoxy-5,6,7-trimethoxyindole and of 1-methyl-5-methoxyindole are described.

In a continuation of our studies of indole compounds related to the physiologically active polyalkoxy-β-phenethylamines,[3–5] we have synthesized several new alkoxyindole derivatives. The present work was undertaken with the idea of synthesizing a number of intermediates which might be used in the preparation of certain key compounds needed for further examining the indole hypothesis of psychotomimetic drug activity.[5]

2,3,4-Trimethoxyaniline (VI) was selected as the starting compound for the new series of indole compounds and a number of routes were investigated for its preparation. As a first approach, it was planned to prepare VI from 2,3,4-trimethxoybenzamide *via* the Hoffmann reaction.[6] However, in attempting to convert 2,3,4-trimethoxyacetophenone[7] to the corresponding benzoic acid *via* the hypohalite oxidation of the side chain,[8] it was noted that considerable nuclear halogenation occurred; the resulting product was believed to be either 5- or 6-chloro-2,3,4-tri-

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