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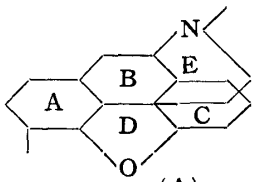
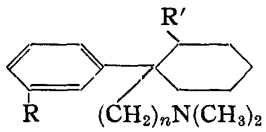
171. Torizo Takahashi, Mikio Hori, and Akio Kanbara : Synthesis of Analgesics. XXV.[1] Aminocyclohexane Derivatives. (11).

(*Pharmaceutical Institute, Medical Faculty, University, of Kyoto,*[*1] *and Gifu College of Pharmacy*[*2])

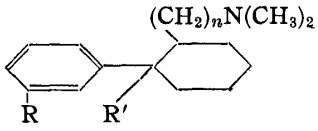
Takahashi and his co-workers have published[2] results on the synthesis of numerous compounds having A-C ring in the morphine skeleton as the basic structure in order to investigate the relationship between the effective partial structure of morphine (A) and its analgesic action, together with the effect on pharmacological activity due to the atomic distance between the quaternary carbon and the tertiary nitrogen in this series. The representative, general formula is shown below.



(A)



(B)



(C)

As is well known with synthetic analgesics in general, compounds possessing a hydroxyl group directly bonded to a benzene ring, in the position *meta* to the quaternary carbon, are more powerful in analgesic activity than those not possessing a hydroxyl group.

In 1955, May and his associates[3] synthesized N,N-dimethyl-1-(*m*-hydroxyphenyl)-cyclohexaneëthylamine (IX) (B : R=OH, R′=H, n=2) and reported the fact that R with methoxyl or substituted hydroxyl group decreased both in activity and toxicity.

Using a different method, (IX) was synthesized in a good yield and its analgesic activity was verified. The present paper reports the synthesis of 1-(1-*m*-methoxyphenylcyclohexyl)trimethylamine (XII), which has 1 carbon less than (IX). The route of this synthesis is given in Chart 1. Ethyl cyclohexylidenecyanoacetate[4] (I) was treated with the Grignard reagent of *m*-bromanisole[5] in benzene and converted to ethyl α-cyano-1-*m*-methoxyphenylcyclohexaneacetate (II). It was then refluxed in an oil bath for 3 hours with potassium hydroxide in ethylene glycol and decarboxylated to 1-*m*-methoxyphenylcyclohexaneacetonitrile (III) which was reduced with lithium aluminum hydride in ether-benzene into 1-*m*-methoxyphenylcyclohexaneëthylamine (IV) in a good yield. (IV) was refluxed for 5 hours in formic acid-formaldehyde solution according to Eschweiler-Clark's method[6] and methylated into N,N-dimethyl-1-*m*-methoxyphenylcyclohexaneëthylamine (VI). (VI) was also obtained by refluxing (III) with potassium hydroxide in ethylene glycol for 6 hours to effect hydrolysis, treated consecutively with phosphorus trichloride, dimethylamine, and lithium aluminum hydride, respectively affording the acetic acid (V), acetyl chloride (VII), and N,N-dimethylacetamide derivatives (VIII), and finally to (VI). The com-

*1 Yoshida-Konoe-cho, Sakyo-ku, Kyoto (高橋酉蔵).
*2 3-chome, Kokonoe-cho, Gifu (堀 幹夫, 神原秋男).

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2) Part XIII. (7)～XVI. (10) : *Ibid.*, **78**, 6, 11, 15, 18(1958).
3) E. May, J. G. Murphy : J. Org. Chem., **20**, 1197(1955).
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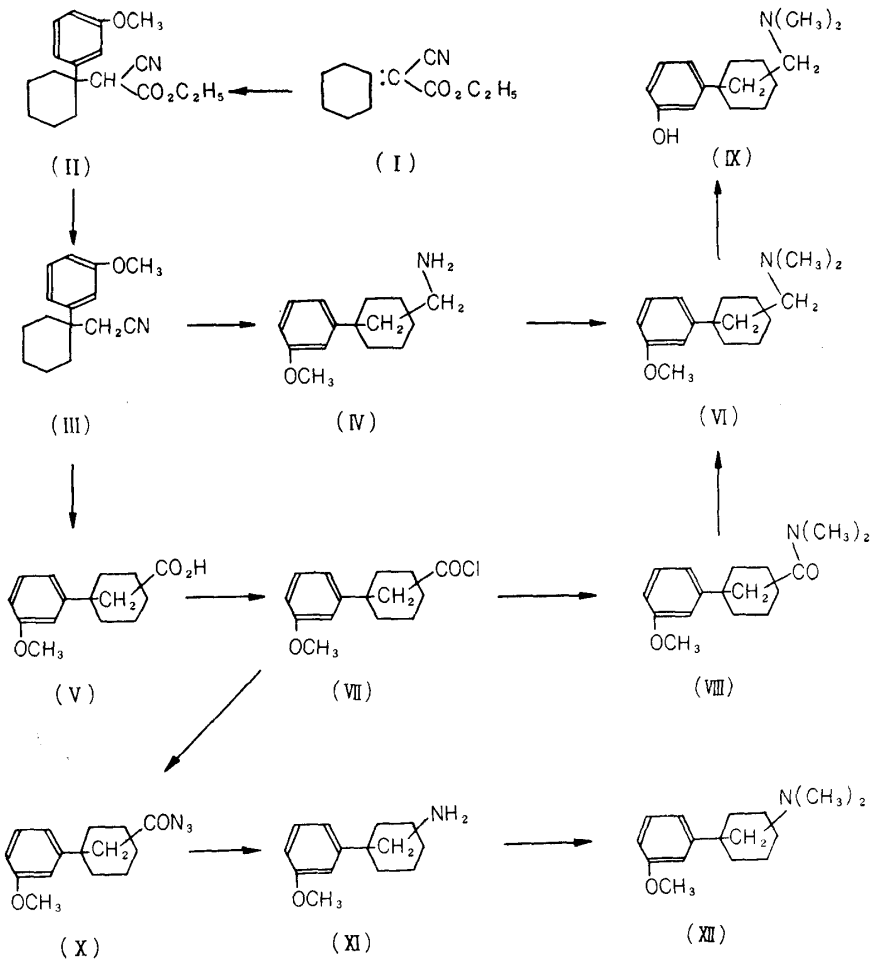

Chart 1.

pounds (V), (VII), and (VIII) were all oily substance. (VI) was treated with an excess of 48% hydrobromic acid and the product showed the same melting point as that of (IX).

(VII) was condensed with sodium azide in hydrous acetone solution and 1-*m*-methoxyphenylcyclohexaneacetyl azide (X) so obtained was hydrolyzed for a few hours with glacial acetic acid and conc. hydrochloric acid, forming 1-*m*-methoxyphenylcyclohexanemethylamine (XI).

Methylation of the amino group in (IX) was conducted by means of the Eschweiler-Clark method.

The pharmacological activity of these compounds was tested by Dr. H. Fujimura and it was found to be extremely small.

The authors thank Dr. Etsuo Miyamichi, President of Gifu College of Pharmacy, for continually giving them encouragement. Thanks are also due to the cooperation of Dr. H. Fujimura and his colleagues in the Department of Pharmacology, University of Kyoto, for the pharmacological tests, and to the members of the Analysis Center, University of Kyoto, for the analytical data. This work was supported by Grant-in-Aid for Developmental Scientific Research from the Ministry of Education, which is gratefully acknowledged.

Experimental

(All m.p.s are uncorrected)

Ethyl α-Cyano-1-*m*-methoxyphenylcyclohexaneacetate (II)—A solution of ethyl cyclohexylidene-

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cyanoacetate (I) (102 g.) in dehyd. benzene (100 g.) was added with stirring to a solution of the Grignard reagent prepared from 1-methoxy-3-bromobenzene (93 g.), Mg (13.2 g.), and dehyd. ether (300 cc.), and the mixture was heated on a steam bath for 1.5 hr. The solvent was substituted with dehyd. benzene (400 cc.), the reaction mixture was refluxed for further 7 hr., cooled, and decomposed with 20% H_2SO_4. The organic layer was separated, dried over anhyd. $MgSO_4$, and the benzene removed. The residue was distilled *in vacuo*. Yield, 90% of almost colorless oil, b.$p_{0.3}$ 187°. *Anal.* Calcd. for $C_{18}H_{23}O_3N$: C, 67.89; H, 8.74. Found: C, 67.90; H, 8.81.

Ethyl α-Cyano-1-*m*-methoxyphenylcyclohexaneacetonitrile (III)—A mixture of the cyanoacetate (II) (84 g.), KOH (32.2 g.), and ethylene glycol (175 cc.) was heated to boiling. After the reaction subsided, it was heated under gentle reflux in an oil bath for about 3 hr. The two-phase mixture was cooled, diluted with H_2O (350 cc.), and extracted with ether. The ethereal layer was washed successively with H_2O (100 cc.) and saturated NaCl solution (100 cc.), and extracted with ether. The ether was evaporated and vacuum distillation of the residue yielded 85% of colorless oil, b.$p_{0.3}$ 175°. *Anal.* Calcd. for $C_{15}H_{19}ON$: N, 6.11, Found: N, 5.96.

1-*m*-Methoxyphenylcyclohexaneëthylamine (IV)—A solution of the acetonitrile (III) (10 g.) in dehyd. ether (400 cc.) was added cautiously to a stirred solution of $LiAlH_4$ (2.6 g.) in dehyd. ether (300 cc.) during 1.5 hr. After the ether was substituted with benzene, the reaction mixture was refluxed for about 3 hr., followed by careful decomposition of the excess hydride with a small quantity of H_2O, freed from inorganic material, and the solvent was evaporated. The residue was dissolved in ether, the ethereal layer extracted with dil. HCl, and the extract basified with an excess of 20% NaOH. This was extracted with ether, which was dried over anhyd. K_2CO_3. Removal of the solvent gave an oily residue, which was treated with dry HCl in dehyd. MeOH. MeOH was removed *in vacuo* and the residue was recrystallized from AcOEt to colorless needles, m.p. 160~161°. Yield, 97%. *Anal.* Calcd. for $C_{15}H_{23}ON \cdot HCl$: C, 66.79; H, 8.91. Found: C, 66.86; H, 9.11.

1-*m*-Methoxyphenylcyclohexaneacetic Acid (V)—A mixture of the acetonitrile (III) (20 g.), KOH (15 g.), and ethylene glycol (200 cc.) was heated under brisk reflux for 6 hr. The reaction mixture was cooled, diluted with H_2O (300 cc.), and extracted with three portions of ether (100 cc). The ether was discarded and the aqueous phase was acidified to Congo Red with conc. HCl, extracted with benzene, and dried over anhyd. $MgSO_4$. After the ether was evaporated, the residue was worked up in the usual manner, but did not crystallize. Yield, 60%.

N,N-Dimethyl-1-*m*-methoxyphenylcyclohexaneëthylamine (VI)—i) From the ethylamine (IV): A mixture of (IV) (9.5 g.), 37% HCHO (1.2 g.), and 80% HCO_2H (1.88 g.) was heated in an oil bath (130°) for 5 hr. After the solution cooled, conc. HCl (20 cc.) was added and evaporated to dryness *in vacuo*. The pale yellow syrupy residue was washed with ether and recrystallized from AcOEt-MeOH to colorless needles, m.p. 159~160°. Yield, 80%. This compound showed a mixed melting point depression with (IV). *Anal.* Calcd. for $C_{17}H_{27}ON \cdot HCl$: N, 4.71. Found: N, 4.45.

ii) From acetic acid (V): (V) (5 g.) was refluxed with PCl_5 (10 g.) in a steam bath for 3 hr. and the mixture was evaporated *in vacuo*. The residue, the acetyl chloride (VII), was dissolved in dehyd. benzene (30 cc.), filtered, treated with a solution of Me_2NH (3 g.) in benzene and the mixture was warmed for about 1.5 hr., followed by dissolution of $Me_2NH \cdot HCl$ with H_2O. The organic layer was dried over anhyd. $MgSO_4$ and concentrated *in vacuo*. An oily residue thereby obtained did not crystallize (the amide (VIII)). Yield, 70%.

This pale yellow syrupy residue (3 g.) was reduced with $LiAlH_4$ (0.6 g.) in the usual manner. Hydrochloride of (VI): Colorless needles (from AcOEt-MeOH), m.p. 160°. Yield, 75%. *Anal.* Calcd. for $C_{17}H_{27}ON \cdot HCl$: C, 68.48; H, 9.43. Found: C, 68.50; H, 9.31.

N,N-Dimethyl-1-*m*-hydroxyphenylcyclohexaneëthylamine (IX)—A solution of the foregoing amine (VI) (5 g.) in 48% HBr (20 g.) was heated in an oil bath (140~150°) for 0.5 hr. HBr was removed *in vacuo* and the crude syrupy residue was recrystallized from Et_2O-EtOH-Me_2CO to colorless needles, m.p. 178°. Yield, 64%. *Anal.* Calcd. for $C_{16}H_{25}ON \cdot HBr$: C, 58.54; H, 8.0. Found: C, 58.38; H, 8.21.

1-*m*-Methoxyphenylcyclohexanemethylamine (XI)—NaN_3 (5 g.) was dissolved in H_2O (50 cc.) and cooled to 0° in an ice bath. This was added to a solution of the acetyl chloride (VII) (5 g.) in acetone (50 cc.) and shaken for 0.5 hr., returning the mixture to the ice bath occasionally to keep the temperature near 0°. The reaction mixture was poured into a beaker containing ice water (300 cc.) and extracted with ether. The organic layer was separated, washed with saturated $NaHCO_3$ solution, and dried over anhyd. $MgSO_4$. Removal of the solvent gave the azide (X) as an oily residue, which was heated with AcOH (60 cc.) for 4 hr. Conc. HCl (80 cc.) was added to the reaction mixture, which was refluxed in an oil bath for 8 hr., the acid solution was basified with 20% NaOH, and extracted with ether. The ethereal layer was dried, evaporated, and the residue distilled. Yield, 90% of almost colorless oil, b.$p_{0.01}$ 102°. *Anal.* Calcd. for $C_{14}H_{21}ON$: N, 6.39. Found: N, 6.30.

1-(*m*-Methoxyphenylcyclohexyl)trimethylamine (XII)—The foregoing amine (XI) (2 g.) was boiled with 80% HCO_2H (3.4 g.) and 37% HCHO (3.5 g.) for 5 hr. and worked up as in the preparation of (VI).

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Hydrochloride: Colorless needles (from MeOH-EtOAc), m.p. 212~214° (decomp.). Yield, 80%. *Anal.* Calcd. for $C_{16}H_{23}ON \cdot HCl$: C, 68.12; H, 8.53; N, 4.96. Found: C, 68.01; H, 8.65; N, 4.72.

Summary

A new synthetic route for N,N-dimethyl-1-*m*-hydroxyphenylcyclohexaneëthylamine (IX) from ethyl cyclohexylidenecyanoacetate is described. 1-(*m*-Methoxyphenylcyclohexyl)trimethylamine(XII) was prepared by the Curtius degradation of 1-*m*-methoxyphenylcyclohexaneacetic acid (V) and subsequent dimethylation.

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172. Goro Chihara*[1] and Keiichi Tanikawa*[2]: Analysis of Compounds containing Heavy Nitrogen (^{15}N) by Infrared Absorption Spectra.

(*Division of Biochemistry, Central Clinical Laboratory,*[*1] *Tokyo University Hospital, and Faculty of Pharmaceutical Sciences, University of Tokyo*)

The use of an isotopic element has become one of the most important measures in studying biochemical and organic reactions. Analysis of radioisotope compounds can be carried out accurately and in a simple manner by the use of a Geiger-Müller, gas-flow, or a scintillation counter. However, analysis of compounds containing stable isotopes like ^{15}N, with the exception of deuterium, had to depend on the mass spectrograph and, consequently, studies using stable isotopes were far behind those using radioactive isotopes.

Infrared spectrophotometer is far more common in laboratories than mass spectrometer and it would be very convenient if stable isotopes could be measured by infrared spectrophotometer. Under such consideration, infrared absorption spectra were measured with ammonium sulfate, *dl*-alanine, phenylalanine, and ephedrine contatining ^{15}N. If strict assingment of absorptions has been determined, infrared spectrophotometer would theoretically be more useful than the mass spectrometer. In compounds examined, those with 6~12% of total nitrogen atoms in ^{15}N did not show any marked isotopic shift. Measurement of compounds with higher percentage of ^{15}N was therefore desired.

A modified apparatus for the Kjeldahl method was therefore devised by combination with the gas cell for infrared spectral measurement so as to convert the sample quantitatively into ammonia and to make the measurement simple and accurate. The apparatus is shown graphically in Fig. 1.

The spectrum obtained by measurement by this means is an overlapping of the absorptions of $^{15}NH_3$ and $^{14}NH_3$, and this makes it possible to prove qualitatively the presence of ^{15}N. Quantitative consideration is also possible.

Establishment of such an apparatus and method will make it possible to carry out analyses of compounds containing isotopic nitrogen in any laboratories equipped with infrared spectrophotometer and open a new field in the study using isotopic elements. However, this method requires a larger quantity of sample than with mass spectrometer and somewhat inferior in accuracy, so that it is not suitable where a slight

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*1 Hongo, Tokyo (千原呉郎).

*2 Present address; Tokyo Institute, Yawata Iron & Steel Works, 1 Marunouchi 1-chome, Chiyoda-ku, Tokyo (谷川啓一).

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