303. *Synthetic Analgesics. Part VI. The Synthesis of Ketobemidone.*

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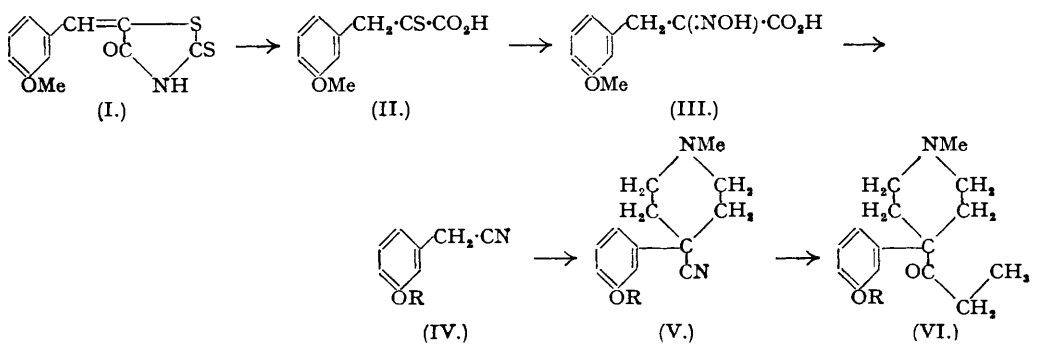
Ketobemidone (Hoechst 10720) has been prepared from *m*-methoxybenzyl cyanide by condensing it with methyldi-(2-chloroethyl)amine in the presence of sodamide, submitting the resulting cyanopiperidine derivative to a Grignard reaction, and demethylating the product with hydrobromic acid.

The analgesic drug, 4-*m*-hydroxyphenyl-1-methyl-4-piperidyl ethyl ketone (VI; R = H), was reported to have been made by Eisleb and his colleagues in the laboratories of the I.G. Farbenindustrie at Hoechst during the war (U.S.A. Office of the Publications Board, Department of Commerce, Report No. PB-981). Under the name ketobemidone (Hoechst No. 10720) it has received pharmacological and clinical investigation (Kirchoff, *Fed. Proc.*, 1948, **7**, 234; Lewis, *J. Pharm. Exp. Ther.*, 1949, **96**, 410; see also *J. Amer. Med. Assoc.*, 1948, **138**, 975), being about ten times as active as pethidine. No details of the synthesis or physical properties of the compound were available at the time of carrying out this work. However, very recently Kägi and Miescher (*Helv. Chim. Acta.*, 1949, **32**, 2489), who refer to F.P. 897,453, which we have been unable to consult, described its preparation by first condensing 3-dimethylamino-1-(*m*-methoxyphenyl)propyl cyanide and 1-chloro-2-bromoethane in the presence of sodamide to give 4-cyano-4-(*m*-methoxyphenyl)-1 : 1-dimethylpiperidinium chloride. This salt was then treated with ethylmagnesium bromide, and methyl chloride removed from the resulting ketone by the action of heat. Demethylation gave (VI; R = H) which the Swiss workers call " Cliradon."



We decided to prepare the ketone by a Grignard reaction on the nitrile (V), which Kägi and Miescher obtained by the action of heat on its methochloride, with suitable protection for the phenolic hydroxyl group.

To prepare *m*-methoxybenzyl cyanide (Chakravati and Rao, *J.*, 1938, 172), necessary for the preparation of (V), we used the rhodanine method starting from *m*-methoxybenzaldehyde (cf. Julian and Sturgis, *J. Amer. Chem. Soc.*, 1935, **57**, 1126). This gave *m*-methoxybenzylidenerhodanine (I) and thence *m*-methoxyphenyl-α-thiopyruvic acid (II) and the oximino-acid (III).

This was not easily isolated in good yield, but the crude product with acetic anhydride underwent dehydration and decarboxylation to give the required *m*-methoxybenzyl cyanide (IV; R = Me) in 52% overall yield from the aldehyde.

Treatment of (IV; R = Me) according to Washington Report PB-981, p. 85, with methyldi-(2-chloroethyl)amine resulted in 4-cyano-4-(*m*-methoxyphenyl)-1-methylpiperidine (V; R = Me). Ethylmagnesium iodide converted this into the ethyl ketone (VI; R = Me) which was readily demethylated with aqueous hydrobromic acid to ketobemidone (VI; R = H).

Experimental.

m-*Nitrobenzaldehyde*.—When a mixture of potassium nitrate and concentrated sulphuric acid was used for the nitration of benzaldehyde according to Ehrlich (*Ber.*, 1882, **15**, 2010) the reaction mixture tended to set to a hard, honey-like consistency at an early stage, thus preventing stirring and making it impossible to work with more than a few grams at a time. The following method was found satisfactory: Concentrated sulphuric acid (850 ml.) was treated with concentrated nitric acid (AnalaR; 500 ml.) with cooling. Urea (1·0 g.) was added and the well-stirred mixture cooled to 0°. Pure benzaldehyde (500 g.) was now added at such a rate as to keep the temperature of the reaction mixture between 0° and 5°. After the addition was complete stirring was continued at 5° for 1½ hours. The mixture was then added to crushed ice (*ca.* 2 kg.) and the pale yellow solid which separated filtered and washed thoroughly with water and finally with light petroleum (b. p. 40—60°). The yield of crude *m*-nitrobenzaldehyde after drying was 86% (619 g.). A single recrystallisation from ether–light petroleum sufficed to purify the compound. It had m. p. 57—58° and was identical with the material prepared according to Ehrlich. For large quantities the crystallisation was best carried out with aqueous acetic acid.

m-*Methoxybenzaldehyde*.—The *m*-nitrobenzaldehyde was reduced in 100-g. batches by the method described in *Org. Synth.* (**25**, 55) and converted into *m*-hydroxybenzaldehyde in yields which were usually below 40%. The latter was methylated according to Lapworth and Shoesmith (*J.*, 1922, 1396).

m-*Methoxybenzylidenerhodanine* (I).—*m*-Methoxybenzaldehyde (54·4 g.) and rhodanine (53·2 g.) were dissolved in hot glacial acetic acid (265 ml.), and powdered anhydrous sodium acetate (120 g.) added. The mixture was boiled gently under reflux with shaking for 30 minutes. The reaction mixture was poured into cold water (2 l.), and the yellow solid product (92 g., 92%) isolated by filtration and washing with water, alcohol, and finally with ether. The *compound* obtained thus was practically pure, having a m. p. of 227—230°. The analytical specimen crystallised from nitrobenzene in yellow plates, m. p. 229—230° (Found: C, 52·6; H, 3·3; N, 5·7. $C_{11}H_9O_2NS_2$ requires C, 52·6; H, 3·6; N, 5·6%).

m-*Methoxyphenyl-α-thiopyruvic acid* (II).—The above rhodanine derivative (23 g.) was heated with 15% aqueous sodium hydroxide (117 ml.) on the water-bath until all had dissolved and then for a further 15 minutes. Cooling in an ice–salt mixture and rapid addition of 10% hydrochloric acid (117 ml.) caused the separation of the *acid* as a dark oil which solidified when rubbed to a yellow solid (17·3 g.), m. p. 90—92°. Recrystallisation from *cyclo*hexane raised the m. p. to 98—99° (Found: C, 57·0; H, 4·5; S, 15·1. $C_{10}H_{10}O_3S$ requires C, 57·1; H, 4·8; S, 15·2%).

α-Oximino-β-(m-methoxyphenyl)propionic Acid (III).—Hydroxylamine hydrochloride (10·5 g.) in water (10 ml.) was added to a solution of sodium (3·5 g.) in absolute alcohol (95 ml.). After removal of the sodium chloride by filtration, the solution was added to *m*-methoxyphenyl-α-thiopyruvic acid (10·5 g.) and the mixture boiled for 3 hours. Concentration *in vacuo* gave a semi-solid residue (in subsequent work this was used directly for conversion into the nitrile) which was dissolved in 1·2N-sodium hydroxide. Acidification of this solution precipitated the *oxime* as a gum which partly crystallised when rubbed and cooled. Ether-extraction of this semi-solid (leaving some sticky material undissolved) and concentration of the extract gave a gum which solidified under benzene. The white solid (3·9 g.) had m. p. 123—125° (decomp.). Recrystallisation from benzene raised the m. p. to 130—132° (decomp.) (Found: C, 57·8; H, 4·7; N, 7·2. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·2; N, 6·7%).

m-*Methoxybenzyl Cyanide* (IV; R = Me).—Owing to the unsatisfactory yield of pure oxime by the method described it was preferable to use the crude concentrated reaction mixture from hydroxylamine and the thio-acid (71·5 g.). Acetic anhydride (200 ml.) was added, with ice-cooling at first to moderate the vigorous reaction, and finally the mixture was warmed on the water-bath until effervescence had ceased. Concentrating the resulting solution *in vacuo*, dissolving the residue in ether, washing with dilute sodium carbonate, drying, and distilling gave the required *m*-methoxybenzyl cyanide (29·5 g.) as a pale yellow oil, b. p. 140—145°/12 mm. (Found: N, 9·35. Calc. for C_9H_9ON: N, 9·5%).

4-(m-*Methoxyphenyl*)-1-*methyl*-4-*piperidyl Ethyl Ketone* (VI; R = Me).—4-Cyano-4-(*m*-methoxyphenyl)-1-methylpiperidine (7·0 g.) was added to the Grignard reagent from magnesium (2·9 g.) and ethyl iodide (19·0 g.) [the ether used in this preparation had been replaced by dry benzene (40 ml.)]. The mixture was boiled with stirring for 16 hours and then cooled and decomposed with ice and ammonium chloride solution. The resulting benzene solution of the intermediate ketimine was hydrolysed by heating it with 2N-hydrochloric acid. After the aqueous layer had been separated and made strongly alkaline the required ketone was precipitated and extracted with ether. Distillation gave a practically colourless oil (2·6 g.), b. p. 130—134°/0·3 mm. (Found: N, 5·6. Calc. for $C_{16}H_{23}O_2N$: N, 5·4%). Kägi and Miescher give b. p. 126—128°/0·02 mm., m. p. 53—55°.

4-(m-*Hydroxyphenyl*)-1-*methyl*-4-*piperidyl Ethyl Ketone* (*Ketobemidone*) (VI; R = H).—The methyl ether (2·5 g.) was demethylated by boiling it with 48% aqueous hydrobromic acid (20 ml.) for 1 hour. The dark solution was concentrated *in vacuo* and the residue dissolved in absolute alcohol. On addition of an equal volume of dry ether to the hot solution and cooling, the hydrobromide (2·4 g.) of the required hydroxyphenylpiperidine derivative separated in light-brown crystals, m. p. 191—192°. Repeated crystallisation from alcohol–ether (charcoal) increased the m. p. to 193—194° (Kägi and Miescher found m. p. 194—196°) but did not remove all the colour (Found: C, 54·4; H, 6·4; N, 4·5; Br^-, 24·6. Calc. for $C_{15}H_{22}O_2NBr$: C, 54·8; H, 6·7; N, 4·3; Br^-, 24·4%).

This compound was obtained equally well by boiling the crude ketimine from the Grignard reaction with 48% aqueous hydrobromic acid. The hydrobromide (3·55 g.) was dissolved in water (15 ml.) and 2N-ammonia (20 ml.) added to precipitate the free base, a practically white solid (2·2 g.), m. p. 150—151° (Kägi and Miescher give m. p. 155—156°) (Found: N, 5·65. Calc. for $C_{15}H_{21}O_2N$: N, 5·7%). Ketobemidone hydrochloride was made by the action of ethereal hydrogen chloride on the base. It had m. p. 196—197° (Found: C, 63·4; H, 7·6; N, 4·9; Cl^-, 12·5. Calc. for $C_{15}H_{22}O_2NCl$: C, 63·5; H, 7·8; N, 4·9; Cl^-, 12·5%). Kägi and Miescher reported m. p. 197·5—199°.

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