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Hydrochloride salts of *N*-substituted-bis-(2-chloroethyl)amines can be condensed with *m*-methoxyphenylacetonitrile or 1-phenyl-2-alkanones under phase-transfer conditions to yield precursors of the powerful analgesic compounds - the ketobemidones.

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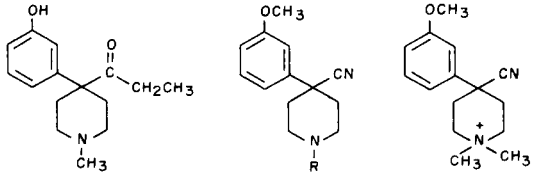
Numerous attempts have been made to synthesize compounds that possess the analgesic properties of the opium alkaloids but that will be less addictive. Among these compounds is ketobemidone (**1**) which was synthesized first in Germany during the 1930's. Pharmacological and clinical investigations have shown it to be about ten times as active as meperidine (Demerol) to which it is structurally related [1].



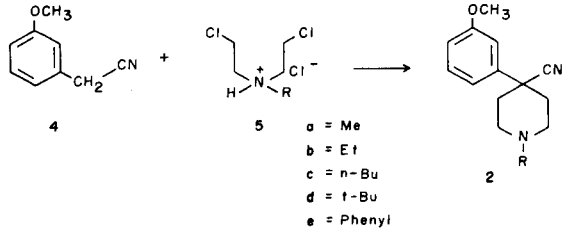
1 **2a** **3**

R = CH_3

Two synthetic sequences for its production have been described. Treatment of *m*-methoxyphenylacetonitrile with *N*-methyl-bis-(2-chloroethyl)amine in the presence of sodamide produced **2a**. Ethylmagnesium iodide converted this into the ethyl ketone which was readily demethylated with aqueous hydrobromic acid to yield **1** [1]. In the second method 4-dimethylamino-2-(*m*-methoxyphenyl)butyronitrile and 1-chloro-2-bromoethane reacted in the presence of sodamide to yield **3**. This salt was then treated with ethylmagnesium bromide and methyl chloride removed from the resulting ketone by the action of heat. Demethylation gave **1** [2]. Because of the inherent difficulties and dangers in the use of sodamide and the complexities of some of the reported procedures, we have attempted to develop a simple synthesis for this important compound.

Within the last decade phase transfer catalysis has become useful as a technique whereby reactions, previously thought to require strong bases in anhydrous solvents, can be carried out in aqueous-organic two phase systems. It was of interest to attempt to apply this method to the dialkylation of *m*-methoxyphenylacetontrile, thus avoiding the use of sodamide. Phase transfer catalysts including quaternary ammonium and phosphonium salts and the macrocyclic ethers were evaluated for their ability to promote the ring closure reaction shown below (Scheme 1). The two most effective catalysts were hexadecyltributylphosphonium bromide (HDTPB) and methyltrioctylammonium chloride (Aliquat). Benzyltriethylammonium chloride (BTEAC) and 18-crown-6 were considerably less effective. Hexadecyltributylphosphonium bromide was used generally because fewer high boiling by-products were formed when it was utilized.

Scheme I



4 **5** **2**

a = Me
b = Et
c = n-Bu
d = t-Bu
e = Phenyl

Typically equimolar quantities of *m*-methoxyphenylacetonitrile (**4**) and the hydrochloride salt of *N*-methyl-bis-(2-chloroethyl)amine (**5a**) were placed in a reaction flask with a catalytic amount of HDTPB and excess fifty percent sodium hydroxide solution. The reaction mixture was stirred vigorously for one hour while being heated at 100°. After extraction and purification by distillation, product **2a** was obtained in 63% yield.

Since this synthesis was successful, it was of interest to attempt to synthesize other *N*-alkyl-4-(*m*-methoxyphenyl)-4-cyanopiperidines. It has been found that varying the *N*-alkyl group of ketobemidone derivatives changes their relative analgesic potencies [3,4]. By using a number of other *N*-substituted-bis-(2-chloroethyl)amine salts, several other derivatives of **2** were produced in yields ranging from 58-70% (Table 1). In the previous work [3,4], the *N*-alkyl substituents were introduced by alkylating the piperidine nitrogen with the appropriate alkyl halide under nucleophilic substitution conditions; therefore, all the *N*-alkyl groups were derived from primary halides. By contrast, our method can produce compounds having a tertiary alkyl or an aromatic *N*-substituent. From these experiments it appears that phase transfer catalysis is an attractive and perhaps superior alternative to the previously described sodamide pathways for the synthesis of ketobemidone intermediates.

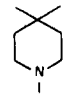
Table 1

Synthesis of *N*-Substituted-4,4-disubstituted Piperidines

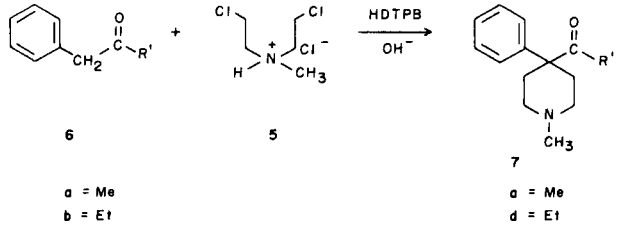
Compound	% Yield	Bp, °C	Mp, °C	Analyses: Calcd. (Found) C		H		N	
2a	63	135°/0.3 mm	—	—		—		—	
2b	60	168°/1.6 mm	—	73.72	(73.83)	8.27	(8.06)	11.47	(11.29)
2c	58	159°/0.3 mm	—	74.93	(74.89)	8.90	(8.95)	10.28	(10.10)
2d	63	142°/0.3 mm	—	74.93	(74.73)	8.90	(9.01)	10.28	(10.05)
2e	70	—	87°	78.04	(77.86)	6.91	(7.04)	9.58	(9.31)
7a	23	98°/0.3 mm	—	77.37	(77.20)	8.83	(9.00)	6.45	(6.20)
7b	26	110°/0.3 mm	—	77.85	(77.78)	9.16	(9.04)	6.05	(6.16)

Table 2

Spectral Properties of *N*-Substituted-4,4-disubstituted Piperidines

Compound	Aryl	$-OCH_3$	NMR (δ) R	R'	
2a	7.02 (m, 4H)	3.78 (s, 3H)	2.35 (s, 3H)	—	2.0-3.2 (m, 8H)
2b	7.10 (m, 4H)	3.81 (s, 3H)	1.13 (t, 3H), 1.52 (q, 2H)	—	2.0-3.2 (m, 8H)
2c	7.05 (m, 4H)	3.80 (s, 3H)	0.93 (t, 3H), 1.25 (m, 4H), 2.20 (t, 2H)	—	2.0-3.2 (m, 8H)
2d	7.10 (m, 4H)	3.85 (s, 3H)	1.15 (s, 9H)	—	2.0-3.2 (m, 8H)
2e	7.10 (m, 4H)	3.84 (s, 3H)	7.10 (m, 5H)	—	2.1-3.7 (m, 8H)
7a	7.34 (m, 5H)	—	2.25 (s, 3H)	1.82 (s, 3H)	2.0-3.8 (m, 8H)
7b	7.27 (m, 5H)	—	2.21 (s, 3H)	0.87 (t, 3H), 2.50 (q, 2H)	2.0-3.7 (m, 8H)

Scheme 2



Using this technique we have also attempted to dialkylate the weakly acidic 1-phenyl-2-alkanones (Scheme 2). If successful, the immediate ketobemidone precursor could be synthesized in a single step. The reactions are carried out as previously described. The crude reaction product distilled over a broad range and a large amount of high-boiling material was obtained. The yields of purified products were low (**7a**, 23%; **7b**, 26%). Spectral and elemental analyses confirmed the production of the desired compounds. It is believed that the low yields result from the low acidity of the ketones and the high reactivity of the aminoalkyl halides. In an attempt to retard the rate of hydrolysis of the halides, the reaction was conducted at room temperature for a period of three hours. Under these conditions no **7** could be detected. Another phase-transfer variation utilized in an attempt to avoid hydrolysis employed dimethylformamide as the solvent and anhydrous potassium carbonate as the base [5]. Once again none of the desired product was formed.

In summary, it appears that phase-transfer catalyzed dialkylation of *m*-methoxyphenylacetonitrile provides a simple and efficient route to the traditional ketobemidone precursors. On the other hand, catalyzed cyclization reactions with the 1-phenyl-2-alkanones appear to hold much less promise.

EXPERIMENTAL

The ^{1}H-nmr spectra were recorded on a Perkin-Elmer R-12B spectrophotometer utilizing deuterated chloroform as the solvent. Chemical shifts are reported in ppm from TMS as an internal standard and are given in δ units. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected.

The *N*-substituted-bis-(2-chloroethyl)amine hydrochlorides have been prepared by a variety of methods [6-8]. The following procedure has been found to give high yields of all the desired salts.

General Preparation of the Hydrochloride Salt of a *N*-Substituted-bis-(2-chloroethyl)amine.

A solution of 0.065 mole of the appropriate *N*-substituted-diethanolamine in 6 ml of chloroform was added dropwise, at room temperature, over a period of 45 minutes to 0.143 mole of thionyl chloride in 8 ml of chloroform. The mixture was refluxed for 1 hour and then chilled. The crystalline material was isolated by suction filtration, washed with ethyl ether and dried. The hygroscopic salts are formed in 70-90% yields. The salts should be handled cautiously since they are severe vesicants.

The following procedure is typical of the phase-transfer catalyzed cyclization reactions.

Preparation of *N*-*t*-Butyl-4-cyano-4-(*m*-methoxyphenyl)piperidine (**2d**).

Into a three-necked, 100-ml round bottom flask equipped with a mechanical stirrer and reflux condenser, was placed 3.00 g (0.020 mole) of *m*-methoxyphenylacetonitrile, 4.87 g (.0021 mole) of *N*-*t*-butyl-bis-(2-chloroethyl)amine hydrochloride, 0.51 g (0.001 mole) of hexadecyltributylphosphonium bromide and 30 ml of 50% aqueous sodium hydroxide. The mixture was stirred vigorously at 100° for one hour. The cooled reaction mixture was transferred to a separatory funnel, diluted with 100 ml of water and extracted with ethyl ether (3 × 50 ml). The ether extracts were washed with water (2 × 50 ml) and extracted with three 50 ml portions of 1:1 mixture of hydrochloric acid and water. The acid extracts were neutralized with solid sodium carbonate and extracted with ether (3 × 50 ml). The ether extracts were dried over anhydrous magnesium sulfate and the ether was evaporated. The residue was vacuum distilled to yield 3.41 g (63%) of the desired product, bp 142-144°/0.3 mm Hg.

Acknowledgement.

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