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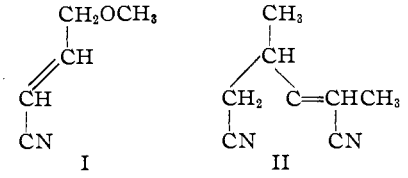
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Syntheses of Certain 3,4-Disubstituted Piperidines[1]

BY C. F. KOELSCH AND S. T. ROLFSON

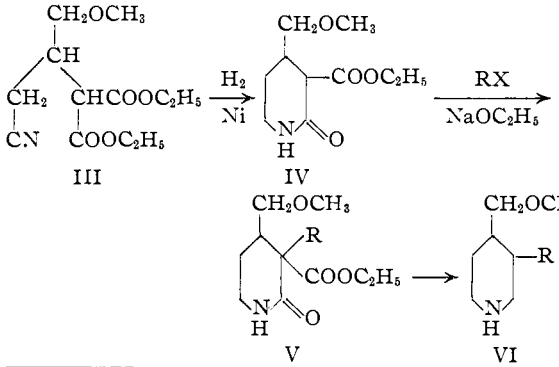
For use in experiments on the synthesis of cinchona alkaloids,[2] derivatives of 3-ethyl-4-methoxymethylpiperidine were needed. The present paper describes some of the methods investigated for the preparation of these substances.

A simple synthesis might be had if γ-methoxycrotononitrile (I) could be caused to dimerize in a fashion analogous to that of crotononitrile. The latter substance yields II,[3] but the former has been found to yield mainly a trimer of unknown structure when it is treated with basic catalysts.



I II

A second route investigated involved compounds III (obtained by adding ethyl malonate to I), IV and V.

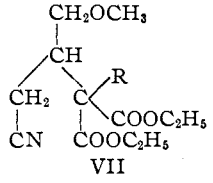


III IV V VI

The piperidines (VI) were then obtained from V by hydrolysis, decarboxylation and sodium–butyl alcohol reduction. Although lactam esters similar to IV have been alkylated,[4] IV itself gave unsatisfactory results. Butyl bromide gave only about 10% of V, R = C_4H_9, β-methoxyethyl *p*-toluenesulfonate gave no alkylated product, and β-phenoxyethyl bromide gave only 23% of V, R = $C_6H_5OCH_2CH_2$, accompanied by considerable C,N-dialkylation product. In these alkylation experiments much of the IV was unchanged.

A third route, involving alkylation of III prior to reductive cyclization was completely unsuccessful. Although III has been alkylated with allyl bromide,[2b] it was recovered unchanged when its sodio derivative was treated with butyl bromide, ethyl bromoacetate, β-phenoxyethyl bromide or β-methoxyethyl *p*-toluenesulfonate.

A fourth route was unexpectedly successful. This involved condensation of I with a monoalkylated malonic ester, giving VII.



VII

General experience has indicated[5] that monoalkylated malonic esters are much less active in Michael reactions than is malonic ester itself. This deactivation was not found in a recent research,[6] nor was it noticeable in the present work, where compounds VII, R = C_2H_5, $CH_3OCH_2CH_2$ and C_2H_5-

(1) From the Ph.D. Thesis of Stanley T. Rolfson, February, 1944.

(2) (a) Koelsch, THIS JOURNAL, **65**, 2460 (1943); (b) **68**, 146 (1946).

(3) Bruylants and Gavaert, *Chem. Centr.*, **94**, II, 1263 (1923).

(4) Koelsch, THIS JOURNAL, **65**, 2458 (1943); Koelsch and Stratton, *ibid.*, **66**, 1883 (1944).

(5) Connor and Andrews, *ibid.*, **56**, 2713 (1934); *J. Org. Chem.*, **6**, 690 (1941).

(6) Floyd, THIS JOURNAL, **71**, 1746 (1949).

OCH_2CH_2, were obtained in 36–50% yields. Subsequent reductive cyclization to V, *etc.*, gave the corresponding piperidines, VI.

Experimental

Polymerization of γ-Methoxycrotononitrile.—The experiments of Bruylants and Gavaert[3] with crotononitrile were checked; a yield of 23% of II being obtained by adding allyl cyanide to sodium ethoxide in warm ether. The same conditions applied to γ-methoxycrotononitrile[2a] gave tarry materials, but when the reaction was carried out at −5° (6.8 g. of sodium ethoxide, 350 ml. of ether, 50 g. of I) during three hours, there was obtained a 37% yield of an oil, b. p. 200–220° at 10 mm. Cooling a solution of this oil in dilute alcohol gave 2.6 g. of a **trimer**, colorless crystals, m. p. 139–140°.

Anal. Calcd. for $C_{15}H_{21}N_3O_3$: C, 61.9; H, 7.2; N, 14.4; mol. wt., 291. Found: C, 62.1; H, 7.4; N, 14.0; mol. wt. (cryoscopic in benzene), 257–290.

Alkylation of IV.—A solution of 4.6 g. of sodium in 30 ml. of absolute alcohol was treated with 43 g. of IV[2a] and 30 g. of butyl bromide. After it had been boiled for two and one-half hours and was neutral, the mixture was distilled to a small volume under reduced pressure. The organic products were isolated by treatment with water and ether and added to 80 ml. of methanol containing 13.2 g. of 85% potassium hydroxide. This solution was boiled for one hour and then neutralized with concd. hydrochloric acid. The potassium chloride and the methanol were removed, and the residue was heated (105°) to cause the piperidone acids to lose carbon dioxide. Fractional distillation then gave 6 g. of crystalline 4-methoxymethyl-2-piperidone, b. p. 134–154° at 2 mm., and 5.5 g. of a mixture of this substance with **3-butyl-4-methoxymethyl-2-piperidone**, b. p. 154–160° at 2 mm.

Anal. Calcd. for $C_{11}H_{21}NO_2$: C, 66.4; H, 10.5. Calcd. for $C_7H_{13}NO_2$: C, 58.7; H, 9.1. Found: C, 63.6; H, 9.6.

The latter fraction (5 g.) was dissolved in 100 ml. of hot butyl alcohol and stirred while 4.6 g. of sodium was added rapidly. The basic products were fractionally distilled, giving 1.9 g. of **3-butyl-4-methoxymethylpiperidine** (VI) R = C_4H_9, b. p. 110–115° at 12 mm. The amine was analyzed as its **picrate**; yellow prisms from alcohol, m. p. 103–104°.

Anal. Calcd. for $C_{11}H_{23}NO + C_6H_3N_3O_7$: C, 49.3; H, 6.3. Found: C, 48.9; H, 5.9.

A similar experiment, and one in which the sodio derivative was prepared and used in xylene, with **β-methoxyethyl *p*-toluenesulfonate**, gave no alkylated piperidone. The sulfonic ester was obtained in 40% yield from methyl cellosolve (140 g.), *p*-toluenesulfonyl chloride (175 g.) and aqueous sodium hydroxide at 10–15°.[7] It distilled with considerable decomposition at 168° at 3 mm., and therefore was purified by low temperature crystallization from ether, m. p. 14–16°.

Anal. Calcd. for $C_{10}H_{14}SO_4$: C, 52.4; H, 6.1. Found: C, 52.4; H, 6.4.

Alkylation of the sodio derivative of IV in xylene with β-phenoxyethyl bromide gave a 14% yield of V, R = $C_6H_5OCH_2CH_2$. Better results were obtained when 21.5 g. of IV in 100 ml. of isopropyl alcohol containing 2.3 g. of sodium was treated with 20.5 g. of β-phenoxyethyl bromide. The mixture was boiled for ten hours, and the sodium bromide was then removed. Aqueous potassium hydroxide (33 g. of 10%) was added, and the solution was boiled for eighteen hours. The neutral material remaining was **ethyl 2-keto-4-methoxymethyl-1,3-bis-β-phenoxyethylnipecotate**; small cubes from ether, m. p. 96–96.5°.

Anal. Calcd. for $C_{26}H_{33}NO_6$: C, 68.6; H, 7.3; N, 3.1. Found: C, 68.7; H, 7.3; N, 3.1.

(7) Compare Norris and Olmstead, "Org. Synthesis," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 138.

The acidic product (6.5 g., 21%) was **2-keto-4-methoxymethyl-3-(β-phenoxyethyl)-nipecotic acid**, colorless crystals from benzene, m. p. 94–95° dec.

Anal. Calcd. for $C_{16}H_{21}NO_5$: C, 62.5; H, 6.8. Found: C, 62.5; H, 7.1.

Decarboxylation of the latter by heat gave **4-methoxymethyl-3-(β-phenoxyethyl)-2-piperidone** as an oil which was obtained crystalline with difficulty; colorless prisms from ligroin, m. p. 74.5–76°.

Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.4; H, 7.9. Found: C, 68.3; H, 8.0.

Reduction of 8.5 g. of the piperidone in 100 ml. of butyl alcohol with 4.6 g. of sodium gave 2.8 of **4-methoxymethyl-3-(β-phenoxyethyl)-piperidine** (VI) R = $C_6H_5OCH_2CH_2$, b. p. 170–180° at 20 mm. The base was analyzed as its **picrate**; small yellow prisms from benzene, m. p. 127.5–128.5°.

Anal. Calcd. for $C_{15}H_{23}NO_2 + C_6H_3N_3O_7$: C, 52.7; H, 5.4. Found: C, 52.5; H, 5.2.

Reactions of I with Monoalkylated Malonic Esters.—A solution of 0.23 g. of sodium in 10 ml. of absolute alcohol was treated with 18.4 g. of ethyl ethylmalonate and 9.7 g. of I. After it had been boiled for twelve hours, the mixture was neutralized with acetic acid and treated with water. Fractional distillation gave 14.8 g. boiling below 112° and 10.1 g. (36%), b. p. 194–196° at 24 mm. The latter, **γ,γ-dicarbethoxy-β-methoxymethylcapronitrile** (VII) R = C_2H_5, solidified. Recrystallization from ether–ligroin gave colorless prisms, m. p. 55–55.5°.

Anal. Calcd. for $C_{14}H_{23}NO_5$: C, 59.0; H, 8.1. Found: C, 58.9; H, 7.9.

Similar experiments using ethyl β-methoxyethylmalonate[8] gave **γ,γ-dicarbethoxy-ε-methoxy-β-methoxymethylcapronitrile** (VII) R = $CH_3OCH_2CH_2$, in yields of 40–50%, unchanged methoxymethylmalonic ester being recovered nearly quantitatively. The product formed colorless prisms from ligroin, m. p. 42–43°, b. p. 168–170° at 4 mm.

Anal. Calcd. for $C_{15}H_{25}NO_6$: C, 57.1; H, 7.9. Found: C, 57.2; H, 7.9.

Ethyl β-ethoxyethylmalonate, b. p. 144–148° at 25 mm. (reported[9] b. p. 152–156° at 16 mm.) gave VII, R = $C_2H_5OCH_2CH_2$ in 42% yield; b. p. 170–172° at 5 mm.

Anal. Calcd. for $C_{16}H_{27}NO_6$: C, 58.4; H, 8.2. Found: C, 58.5; H, 8.4.

3-β-Methoxyethyl-4-methoxymethylpiperidine (VI) R = $CH_3OCH_2CH_2$.—Compound VII, R = $CH_3OCH_2CH_2$, (31.5 g.) in 55 ml. of absolute alcohol absorbed the calculated amount of hydrogen in five minutes at 150° and 160 atm. in the presence of Raney nickel. Catalyst and alcohol were then removed, and the oily product was boiled for five hours with 7 g. of potassium hydroxide in 70 ml. of water. The saponified material was removed and heated at 120° to effect decarboxylation. The crude piperidone was reduced in 250 ml. of butyl alcohol with 23 g. of sodium. There was obtained 8 g. of product (43%), b. p. 146–150° at 30 mm. The **picrate** formed yellow needles from ethyl acetate–ligroin, m. p. 99–99.5°.

Anal. Calcd. for $C_{10}H_{21}NO_2 + C_6H_3N_3O_7$: C, 46.1; H, 5.8. Found: C, 46.3; H, 5.7.

The chloroplatinate formed crystals from alcohol, m. p. 136–138° dec.

Anal. Calcd. for $C_{10}H_{21}NO_2 + H_2PtCl_6$: C, 20.1; H, 3.9; Pt, 32.6. Found: C, 19.7; H, 3.6; Pt, 33.0.

3-β-Ethoxyethyl-4-methoxymethylpiperidine (VI) R = $C_2H_5OCH_2CH_2$.—From 63.5 g. of VII, R = $C_2H_5OCH_2CH_2$, by an analogous series of treatments, there was obtained 18 g. (46%) of amine, b. p. 139–140° at 15 mm.

(8) From β-methoxyethyl *p*-toluenesulfonate in 55–60% yield, b. p. 142–144° at 29 mm. Palomaa and Kenetii report b. p. 110–111° at 6 mm.; *Ber.*, **64**, 797 (1931).

(9) Prelog and Bozicevic, *ibid.*, **72**, 1103 (1939).

Anal. Calcd. for $C_{11}H_{23}NO_2$: C, 65.6; H, 11.4. Found: C, 65.3; H, 11.3.

The chloroplatinate formed a light tan powder from dilute alcohol, m. p. 165–166° dec.

Anal. Calcd. for $C_{11}H_{23}NO_2 + H_2PtCl_6$: N, 2.6. Found: N, 2.5.

Summary

Several methods for the preparation of 3-substituted-4-methoxymethylpiperidines have been studied. The best one involves condensation of γ-methoxycrotononitrile with a monoalkylated malonic ester, where 36–50% yields are obtained. Subsequent steps, reductive cyclization, hydrolysis, decarboxylation and sodium–butyl alcohol reduction can be effected, without isolating intermediates, in yields of 43–46%.

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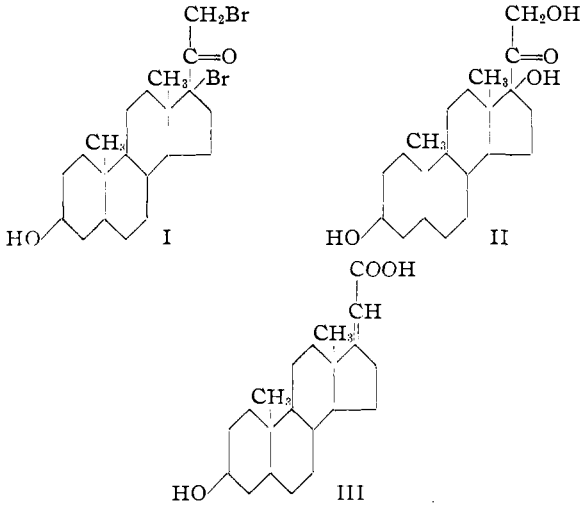
[CONTRIBUTION FROM THE WHITMORE LABORATORIES OF THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Some Metathetical Reactions of α,α'-Dibromomethyl Cyclohexyl Ketone

BY R. B. WAGNER AND JAMES A. MOORE[1]

The direct hydrolysis of 17,21-dibromopregnan-20-one compounds (I) to the corresponding diols (II) would represent a very valuable route in the elaboration of the side-chain of the cortical hormones.



This dibromoketone system, however, exhibits a strong tendency toward rearrangement, when treated with alkali hydroxides, with the formation of the pregnenoic acid (III)[2]; hydrolysis to the dihydroxyketone has never been accomplished. An aliphatic α,α'-dibromoketone, 2,4-dibromo-2,-4-dimethyl-3-pentanone, in which both bromine atoms are tertiary, has been converted to the dihydroxyketone in unstated yield by treatment with aqueous potassium carbonate.[3] In this case, no rearrangement products were reported.

In the present work, this problem of the hydrolysis and related metathetical reactions of an α,α'-dibromoketone has been further investigated. The compound chosen for this study was the α,α'-dibromo derivative of methyl cyclohexyl ketone. This compound was desirable from two standpoints; it had been synthesized by two independent routes[4] and its structure was thus positively known, and it represented a model compound for the dibromoketone of the steroid series (I). α,α'-Dibromomethylcyclohexyl ketone and several analogous ketones have been found previously to yield exclusively α,β-unsaturated esters upon treatment with sodium methylate in ether, *viz.*, $R_2CBrCOCH_2Br \rightarrow R_2C{=}CHCO_2CH_3$.[4]

Upon treatment with aqueous potassium hydroxide or potassium carbonate, however, this compound has been found to yield approximately equal amounts of the rearrangement product, cyclohexylideneacetic acid, and the metathesis product, α,α'-dihydroxymethyl cyclohexyl ketone. The yields of these compounds were quite low due to the difficulty of obtaining complete removal of the bromine atoms without causing serious decomposition of the products.

The reaction of the dibromoketone with sodium benzoate under two sets of conditions was also investigated. When a benzene–xylene mixture was employed as the medium, the only product which could be isolated (in very poor yield) was the benzoate of hydroxymethyl α-bromocyclohexyl ketone, thus only the primary bromine atom was attacked. When benzoic acid was used as a solvent, the product was the benzoate of hydroxymethyl 1-cyclohexenyl ketone, in which both bromine atoms had been abstracted.

These reactions and the interconversions which were made in order to characterize the products are summarized in the accompanying chart.

The behavior of this dibromoketone may be compared with the 17,21-dibromopregnan-20-one series. In addition to the contrasting effects of alkaline reagents, the action of sodium benzoate in benzoic acid in the present study is somewhat different from that of potassium acetate in acetic acid on the dibromo steroidal ketone.[5] In the latter case, the tertiary bromine atom is preferentially removed with the formation of the 21-bromo-16,17-unsaturated compound.

(1) Present address: Research Department, Parke, Davis and Company, Detroit, Michigan.

(2) Marker, Crooks and Wagner, THIS JOURNAL, **64**, 817 (1942).

(3) Favorskii, *J. prakt. Chem.*, [2] **88**, 681 (1913).

(4) Wagner and Moore, THIS JOURNAL, **72**, 974 (1950).

(5) Marker, Crooks and Wagner, *ibid.*, **64**, 213 (1942).