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AN IMPROVED SYNTHESIS OF PILOCARPINE

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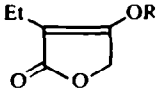
Abstract—Michael condensation of diethyl ethylmalonate with 2-oxo-5-ethoxy-2,5-dihydrofuran (**12**) followed by treatment with hot hydrogen bromide-acetic acid afforded 2-ethyl-3-carboxymethylbutenolide (**10b**). Hydrogenation as the ester (**10a**) followed by acid hydrolysis yielded DL-homopilopic acid, the key intermediate for the synthesis of pilocarpine.

THE ALKALOID, PILOCARPINE, is no longer used extensively as a medicinal agent, however, it still enjoys some utility for veterinary and opthalmological purposes. As part of a program designed to develop synthetic processes for various drugs of natural origin we have formulated a new and improved synthesis of pilocarpine. Preobrazhenski *et al.* in a series of publications[1-5] and Dey[6] have previously described syntheses of pilocarpine. We have repeated both of these methods and found them to be lengthy and impractical. In addition, some key steps in Dey's process could not be reproduced.

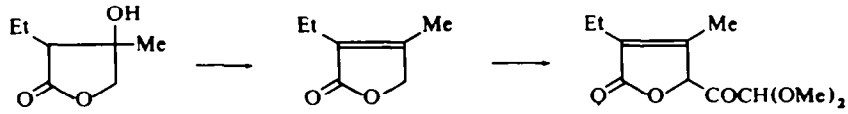
The pilocarpine molecule contains a γ-lactone with substituents at the α and β positions which are of *cis*-stereochemistry. The *cis* compounds can be transformed into the *trans* isomers by the action of heat or alkaline media.[1, 6, 7] Previous syntheses involved a tedious separation of *cis* and *trans* isomers from mixtures which were predominantly *trans*, with consequent low yields. We sought to improve upon this situation by preparing an α,β-unsaturated lactone intermediate which could be converted by catalytic hydrogenation to a predominantly *cis* mixture of isomers, thus facilitating the separation of *cis* material. The synthesis of the key intermediate, homopilopic acid (**11**), by such a method is the main subject of this paper. The subsequent conversion of 11 to DL-pilocarpine by a variation of the general method of Preobrazhenski *et al.*,[4, 5] is also described.

Several routes were investigated for the preparation of an α,β-unsaturated γ-lactone intermediate capable of conversion to pilocarpine. The first involved condensation of the tosylate (**2**) of α-ethyltetronic acid[8] (**1**) with diethyl sodiomalonate. The desired Michael addition with subsequent elimination of tosylate was not observed. The major product in EtOH was ethyl tosylate, while in THF, no identifiable products were obtained. Attempts to prepare the ether (**3**) by a variety of methods were unsuccessful. Considerable high-boiling material, apparently of a dimeric nature, was obtained along with several other unidentified products.



1: R = H
2: R = Ts
3: R = Me

A second unsuccessful approach began with the Reformatski condensation of ethyl 2-bromobutyrate and acetoxy acetone. The resulting hydroxy lactone (**4**) was dehydrated to the α-ethyl-β-methylbutenolide (**5**), which was condensed with methyl dimethoxyacetate and NaH in ether with the hope of obtaining acylation on the β-methyl group. However, NMR data indicated that reaction occurred on the γ-carbon to form **6**. The methyl signal at 8·00 τ as seen in **5** was retained, while the 5·49 τ band for the C-5 CH_2 group disappeared.

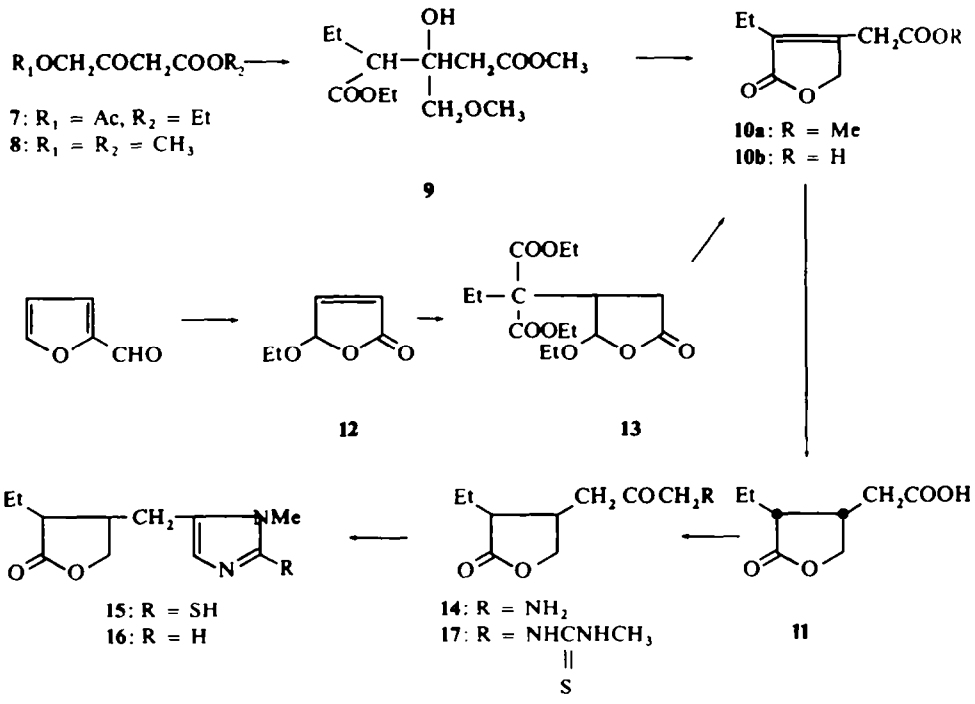


4 **5** **6**

A variation of this route was the Reformatski reaction of ethyl 2-bromobutyrate with ethyl 4-acetoxyacetoacetate (**7**). No identifiable product was obtained from this reaction, but when **7** was replaced by methyl 4-methoxyacetoacetate[9] (**8**), the hydroxy diester (**9**) was isolated. Considerable 4-methoxyacetoacetate was recovered due to enolization during the reaction, which acts to consume Zn reagent by formation of the bromo zinc enolate salt of **8** and ethyl butyrate.[10] The crude hydroxy ester (**9**) was dehydrated with conc. H_2SO_4 at 155-165° to yield the butenolide ester (**10a**). Hydrogenation of the unsaturated lactone over 5% rhodium-on-carbon followed by acid hydrolysis of the ester group afford DL-homopilopic acid (**11**) in a 37% yield after recrystallization. The material was identical with a sample prepared by the method of Preobrazhenski *et al.*[1, 4]

A more efficient process for the preparation of homopilopic acid was initiated with furfural. Air oxidation of an ethanolic solution of furfural in the presence of sunlight[11] gave 2-oxo-5-ethoxy-2,5-dihydrofuran (**12**) in a 44% yield. Michael condensation of **12** with diethyl ethylmalonate afforded the lactone ester (**13**) in a 99% yield. Prolonged treatment of **13** with hot HBr in AcOH gave an 88% yield of the acid (**10b**) which was converted to the methyl ester (**10a**) and hydrogenated as above.

Preobrazhenski *et al.*,[4, 5] have previously converted homopilopic acid (**11**) to pilocarpine by proceeding through the amino methyl ketone (**14**), which was then condensed with methyl isothiocyanate to give 2-mercapto-pilocarpine (**15**). Desulfurization of **15** with peroxide or $FeCl_3$ afforded DL-pilocarpine (**16**). The Russian workers prepared the amino ketone in a 28% yield from **11**, by proceeding through the chloro and phthalimidomethyl ketones. Our own procedure for the synthesis of 14 involved condensation of the acid chloride of **11** with sodio di-t-butyl acetamidomalonate[12] followed by acid hydrolysis and decarboxylation of the resulting keto malonate intermediate. The yield for this process was 49%, however, it required the preparation of di-t-butyl acetamidomalonate, which is not a convenient undertaking at present. Since the Russian group[5] did not give any yield or experimental details for the conversion of **14** to **16** we have included our procedures for these reactions in the experimental section. The optical resolution of racemic pilocarpine with tartaric acid is described by Dey.[6]



EXPERIMENTAL

M.ps were taken with a Fischer-Johns apparatus and are corrected. A Perkin-Elmer Infracord was used for the IR spectra.

2-Oxo-3-ethyl-4-tosyloxy-2,5-dihydrofuran (**2**). To an ice cold solution of 0·34 g of 2-ethyltetronic acid (**1**)[8] in 1·0 ml of pyridine was added 0·55 g of TsCl. The solution was allowed to stand for 1 hr at room temperature and was evaporated to dryness *in vacuo*. The residue was stirred with 10 ml of H_2O and the white crystals were collected, washed with H_2O and dried to leave 0·66 g (88 %). Recrystallization from 10 ml cyclohexane–1 ml C_6H_6 afforded 0·58 g, m.p. 107 108°. (Found: C, 55·4; H, 5·22; S, 11·3. Calc. for $C_{13}H_{14}O_5S$: C, 55·3; H, 4·99; S, 11·4 %).

2-Ethyl-3-hydroxy-3-methylbutyrolactone (**4**). A vigorously stirred mixture of 29·0 g (0·25 mole) of acetonyl acetate, 20 g (0·3 g atom) of Zn dust and 300 ml of C_6H_6 (containing a catalytic amount of I_2) was heated to boiling. Then 53 g (0·27 mole) of ethyl 2-bromobutyrate was added over 30 min at such a rate that a moderate reflux was maintained. The mixture was refluxed another 45 min and cooled in an ice bath. Ice water (200 ml) was added followed by 60 ml of 6N HCl. The mixture was stirred until two clear phases were present plus a little unreacted Zn. The layers were separated and the aqueous portion extracted with two 75-ml portions of ether. The combined organic extracts were washed with 100 ml of sat. $NaHCO_3$ and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to leave 29·6 g which was distilled to give 16·3 g (45 %), b.p. 98–100° 1·6 mm; λ_{max}^{film} 2·90 μ (OH), 5·60, 5·75 (lactone (C=O)), 9·80 (C–O–C). (Found: C, 58·6; H, 7·93. Calc. for $C_7H_{12}O_3$: C, 58·3; H, 8·39 %).

2-Oxo-3-ethyl-4-methyl-2,5-dihydrofuran (**5**). A mixture of 9·0 g of the hydroxylactone (**4**) and 0·30 g of TsOH was heated at 150° for 15 hr. The dark syrup was distilled through a short path to afford 5·2 g (66 %) of clear liquid, b.p. 76 78°/1·1 mm; λ_{max}^{film} 5·75 μ (lactone C=O), 6·00 (C=C), 9·70 (C–O–C). NMR in CCl_4; 5·49 τ (2H's on C-5), 8·00 (Me on C-4). (Found: C, 66·5; H, 8·00. Calc. for $C_7H_{10}O_2$: C, 66·6; H, 7·99 %). When 5 was condensed with methyl dimethoxyacetate and NaH in ether the strong Me signal at 8·00 τ was retained while the 5·49 signal for the C-5 CH_2 disappeared, which indicated the product to be **6**.

Ethyl 4-acetoxyacetoacetate (**7**). A solution of 80 g of ethyl 4-bromoacetoacetate[1,9] and 72 g of anhyd.

NaOAc in 500 ml of HOAc was heated at 85–90° for 6 hr. The solution was evaporated to dryness *in vacuo* and the residue was treated with 400 ml of CH_2Cl_2, followed by storage at 0° for 2 hr. The salts were filtered off, the filtrate evaporated and the residual liquid distilled to afford 27·4 g (38%) at b.p. 106–108°/2·2 mm. A redistillation for analysis gave b.p. 84–86°/0·7 mm. TLC showed a single spot, free of the bromo ester. Ratusky and Sorm[14] prepared this compound by a less convenient procedure and observed b.p. 70°/0·1 mm. (Found: C, 50·5; H, 6·21. Calc. for $C_8H_{12}O_5$: C, 51·1; H, 6·43%).

2-Oxo-3-ethyl-4-carbomethoxymethyl-2,5-dihydrofuran (**10a**). A mixture of 39 g (0·27 mole) of methyl 4-methoxyacetoacetate,[9] 43 ml (0·32 mole) of ethyl 2-bromobutyrate, 22 g (0·34 g atom) of 20 mesh Zn amalgam and 300 ml of C_6H_6 (containing a catalytic amount of I_2) was heated with stirring until reaction commenced. The heat was removed and reapplied in a few minutes after the most vigorous phase of the reaction subsided. The mixture was stirred at reflux for 3·25 hr, cooled in ice, treated with 300 ml of water and acidified with 60 ml of 6N HCl. Stirring was continued until two clear phases were present. They were separated and the aqueous phase was extracted with two 60-ml portions of $CHCl_3$. The organic extract was washed with 50 ml of sat. $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue heated at 70°/0·5 mm to afford 25 g of distillate (methoxyacetoacetate) and 12·1 g of residue, regarded as the hydroxy ester intermediate (**9**); λ_{max}^{film} 2·90 μ (OH), 5·7–5·8 (ester C=O), 9·8 (C–O–C). The yield was 17% or 48% based on recovered methoxyacetoacetate. The 25 g of recovered material was again reacted with bromobutyrate to yield another 6·8 g of **9**.

The hydroxy ester (18·9 g) and 1 ml of conc. H_2SO_4 was heated at 155–165° for 10 hr, allowing all volatiles to distill out of the vessel. The dark residue was partitioned between 150 ml of ether and 25 ml of saturated $NaHCO_3$. The $NaHCO_3$ solution was extracted with three 25-ml portions of ether and the combined ether extracts were dried over $MgSO_4$ and evaporated *in vacuo* to leave 8·0 g. Distillation at reduced pressure yielded 5·5 g (41%) of **10a**, b.p. 110–120°/0·5 mm; λ_{max}^{film} 5·68–5·75 μ (lactone, ester C=O), 5·97 (C=C), 9·63 (lactone C–O–C), 12·85 (C=C). An analytical sample had b.p. 128°/1·1 mm. (Found: C, 58·6; H, 6·37. Calc. for $C_9H_{12}O_4$: C, 58·7; H, 6·57%).

Homopilopic acid (**11**). A mixture of 6·2 g of the unsaturated lactone ester (**10a**), 2·5 g of 5% Rh/C and 40 ml of EtOH was stirred under an atmosphere of H_2 at ambient temperature for 72 hr. The calculated amount of gas was consumed. The catalyst was removed by filtration and the solvent removed *in vacuo*; λ_{max}^{film} 5·65 μ (lactone C=O), 5·75 (ester C=O), 5·97 and 12·85 removed.

The dihydro ester (5·92 g) was refluxed with 60 ml of 4N HCl for 4 hr. The solution was evaporated to dryness *in vacuo* and 20 ml of C_6H_6 was added and evaporated. The residue was taken up in 30 ml of ether, dried over $MgSO_4$ and the ether solution diluted with 16 ml of hexane. The solution was chilled at −5° for 15 hr to afford 2·00 g (37%) of crystalline homopilopic acid (**11**), m.p. 98–101°. The IR spectrum was identical to that of material prepared by Preobrazhenski's method[1, 4] and showed no evidence of isohomopilopic acid; the two acids differ considerably in the 9·5–10·5 μ region. Material from another run was crystallized from ether to m.p. 104–105°. Admixture with authentic material (m.p. 103·5–104·5) gave no depression, m.p. 103·5–105°.

2-Oxo-5-ethoxy-2,5-dihydrofuran (**12**). A quartz tube charged with 5·0 g of furfural, 200 mg of eosin and 40 ml of EtOH was exposed to sunlight for 33 hr while air was bubbled through the solution. The solvent was distilled off at reduced pressure and the product, 2·9 g (44%), was collected at 85–89°/8 mm; λ_{max}^{film} 3·27 μ (C=C), 5·55, 5·65 (C=O), 5·90 (C=C). A 23% yield was obtained from a 125 g scale run. Ogura[11] reported b.p. 93–97°/10 mm and an 80% yield when certain antioxidants were added to the reaction medium.

3-(1,1-Dicarbethoxy-1-propyl)-4-ethoxybutyrolactone (**13**). To 13·6 g (0·168 mole) of diethyl ethylmalonate was added 0·34 g (0·015 g atom) of Na and the mixture was stirred at 100° until the Na disappeared. The solution was cooled to 5° in an ice bath and 21·5 g (0·168 mole) of the pseudo-lactone (**12**) was added over 25 min, keeping the temperature below 20°. After neutralization with HOAc the mixture was partitioned between 100 ml of ether and 50 ml of water. The aqueous phase was saturated with NaCl and extracted twice with 40 ml portions of ether. The ether extract was washed with 30 ml of saturated $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the solvent left 47·7 g (99%) of a light amber syrup; λ_{max}^{film} 5·55 μ (pseudo-lactone C=O), 5·76 (ester C=O), *no* C=C remained. An analytical sample, b.p. 160–163°/1·5 mm was obtained from another run. The IR spectrum was identical to the above crude material. (Found: C, 56·9; H, 7·66. Calc. for $C_{15}H_{24}O_7$: C, 56·9; H, 7·65%).

2-Oxo-3-ethyl-4-carboxymethyl-2,5-dihydrofuran (**10b**). The pseudo-lactone diester (**13**), 589 mg, and 2 ml

* NMR analysis confirmed that bromination of ethyl acetoacetate yields 96% of 4-bromo and 4% of 2-bromoacetoacetate as observed by Kharasch *et al.*

of 30% HBr in HOAc was refluxed 48 hr. The solution was evaporated to dryness *in vacuo* and the dark residue extracted with ether. The ether was dried over $MgSO_4$ and evaporated to leave 279 mg (88%). The IR spectrum showed about 10-15% of the 5·55 band remaining, but longer heating would not improve upon this. The spectrum was very similar to that of the methyl ester (**10a**).

Esterification with CH_2N_2 afforded the ester (identified by IR and thin layer comparison with **10a**), but the *ca.* 10% contamination by the 5·55 μ material was still present. Esterification with *p*-TsOH and MeOH at reflux for 3 hr gave material identical with **10a**; the 5·55 band could not be detected. In a large-scale run a 70% over-all yield of ester (**10a**) was obtained, starting from **13**.

Aminomethyl homopilopyl ketone (**14**). A mixture of 2·9 g (0·0106 mole) of di-t-butyl acetamidomalonate,[1,2] 0·48 g (0·0112 mole) of 56% NaH in oil, 0·05 ml of t-amyl alcohol and 27 ml of C_6H_6 was stirred at reflux for 4·5 hr. A solution of 2·0 g (0·0116 mole) of homopilopic acid (**11**) in 13 ml of $SOCl_2$ was refluxed 3 hr and evaporated to dryness *in vacuo*, followed by the addition and evaporation of two 10-ml portions of toluene. The residual acid chloride, in 20 ml of C_6H_6, was added dropwise to the sodio t-butyle malonate mixture above at room temp. The mixture was stirred at reflux for 2 hr, cooled to room temp., treated with a few chips of Dry Ice and partitioned between 20 ml of H_2O and 20 ml of ether. The aqueous phase was extracted with another 30 ml of ether and the combined ether extracts were washed with 20 ml of st. $NaHCO_3$ and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the syrup was washed with 30 ml of warm hexane. The hexane insoluble residue was dried to leave 4·21 g (93%) of keto malonate intermediate. The syrup was refluxed with 60 ml of 3N HCl for 5 hr, evaporated to dryness *in vacuo* and 20 ml of abs. EtOH added and evaporated to leave 2·49 g. The crude aminoketone hydrochloride was washed with 20 ml of ether and treated with 15 ml of acetone to cause crystallization. After 2 days the white crystals were collected, washed with acetone and dried to leave 1·16 g (49%). For analytical purposes the picrate salt was prepared in H_2O and recrystallized from 95% EtOH to give yellow crystals, m.p. 155-156·5°. (Found: C, 43·7; H, 4·41; N, 13·3. Calc. for $C_{15}H_{18}N_4O_{10}$: C, 43·5; H, 4·38; N, 13·5%).

For comparison purposes the aminoketone from isohomopilopic acid was prepared in the same manner as for **14**. The picrate was recrystallized from 90% EtOH to give yellow crystals, m.p. 162-163°. (Found: C, 43·4; H, 4·33; N, 13·8. Calc. for $C_{15}H_{18}N_4O_{10}$: C, 43·5; H, 4·38; N, 13·5%).

The IR spectra of the isoaminoketone hydrochloride and picrate were significantly different from those of the *cis*-isomer (**14**).

DL-2-Mercaptopilocarpine (**15**). A mixture of 1·20 g of K_2CO_3, 2·0 g of CH_3NCS, 1·90 g of **14** and 25 ml of 70% THF was stirred at ambient temperature for 16 hr. The solvent was removed *in vacuo* and the residue was dissolved in 5 ml of H_2O and extracted with two 10-ml portions of n-BuOH. The BuOH was dried over $MgSO_4$ and evaporated *in vacuo* to leave 1·38 g of a syrup. The IR showed two carbonyl bands at 5·65 and 5·75 μ. The syrup was heated 20 min with 10 ml of HOAc, which was evaporated and the residue crystallized from 4 ml of iso-PrOH to give 0·90 g (43%), m.p. 261-264°. Preobrazhenski *et al.*,[5] reported m.p. 253-255°. The HOAc treatment probably effects cyclization of the intermediate (**17**) to the imidazole (**15**). (Found: C, 54·8; H, 6·75; N, 11·6. Calc. for $C_{11}H_{16}N_2O_2S$: C, 55·1; H, 6·72; N, 11·7%).

DL-Pilocarpine (**16**). A mixture of 155 mg of DL-2-mercaptopilocarpine, 1/4 tsp of Raney nickel and 3 ml of 2-methoxyethanol was stirred at 100° for 2 hr. The nickel was removed by centrifugation and the solvent evaporated. The residue was dissolved in 5 ml of H_2O and the solution adjusted to pH 8 with 40% KOH. Three extractions with 5 ml portions of $CHCl_3$ yielded 47 mg of syrup which was identical to the free base of natural pilocarpine in the IR. A sample of the hydrochloride salt, m.p. 204-208°, was isolated from another run. Preobrazhenski[5] reported m.p. 208-209° for DL-pilocarpine hydrochloride.

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REFERENCES

1. A. E. Tschitschibabin and N. A. Preobrazhenski, *Ber. Dtsch. Chem. Ges.* **63**, 460 (1930)
2. N. A. Preobrazhenski, A. F. Wompe, W. A. Preobrazhenski and M. N. Schtschukina, *Ibid.* **66**, 1536 (1933)
3. N. A. Preobrazhenski, A. M. Poljakowa and W. A. Preobrazhenski, *Ibid.* **68**, 844 (1935)
4. N. A. Preobrazhenski, A. M. Poljakowa and W. A. Preobrazhenski, *Ibid.* **69**, 1835 (1936)
5. N. A. Preobrazhenski, M. E. Maurit and G. V. Smirnova, *Doklady Adad. Nauk SSSR* **81**, 613 (1951)
6. A. N. Dey, *J. Chem. Soc.* 1057 (1937)
7. Jowett, *Proceed. Chem. Soc. London* **21**, 172 (1905)
8. E. B. Reid, R. B. Fortenbaugh and H. R. Patterson, *J. Org. Chem.* **15**, 572 (1950)

[9] W. J. Brehm and T. Levenson, *J. Am. Chem. Soc.* **76**, 5389 (1954)
[10] M. Newman, *Ibid.* **62**, 870 (1940)
[11] I. Ogura, Japan 6314, July 28, 1956; *Chem. Abs.* **52**:11910 (1958)
[12] A. W. Schrecker and M. Trail, *J. Am. Chem. Soc.* **80**, 6077 (1958)
[13] M. S. Kharasch, E. Sternfeld and F. R. Mayo, *Ibid.* **59**, 1655 (1937)
[14] J. Ratusky and F. Sorm, *Chem. Listy* **51**, 1091 (1957); *Chem. Abs.* **51**:13843 (1957)