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AZAPROSTANOIDS I. SYNTHESIS OF (RAC)-11-DESOXY-12-AZAPROSTANOIDS.[1]

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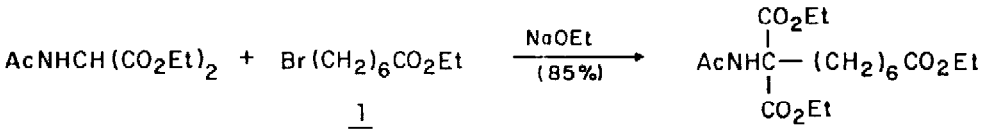
As part of our continuing interest in nitrogen analogs of prostaglandins,[2] we have synthesized prostanoids[3] in which a nitrogen atom replaces C-12 of the five-membered ring.[4]

2-Aminoazaleic acid dimethyl ester hydrochloride[5] (2), m.p. 113-18°, was prepared by a new, three-step synthesis starting from ethyl 7-bromoheptanoate (1) and diethyl acetamidomalonate. Although the N-acetyl, N-benzoyl, and N-carbobenzoxy derivatives of 2 were obtained as oils, the p-phenylbenzoyl (BPCO) derivative 3 was a crystalline solid, m.p. 72-3°. Treatment of amide 3 with NaH/DMF and methyl acrylate gave a mixture of carbomethoxy substituted pyrrolidones 4. Selective decarbomethoxylation of these β-keto esters with NaCl in DMSO[6] at 140° gave pyrrolidone 5, m.p. 90-2°, ν_{max} 1752, 1728, 1625, 1610 cm^{-1}. Conversion of this to the dimethyl ketal 6 followed by reductive removal of the BPCO protective group with 3% sodium amalgam in methanol at about 25° gave racemic [7] amino ketal 7 as a mobile liquid [81%; pmr δ 3.60 (s, 3, CO_2CH_3), 3.20 (s, 3, OCH_3), 3.13 (s, 3H, OCH_3; HRMS calcd. for M^+ of $C_{14}H_{27}NO_4$ 273.1938, meas. 273.1939].

Conversion of hindered amide 6 to amine 7 by known methods for the hydrolysis of amides proved either ineffective or required such vigorous conditions as to give mainly tars. Reductive cleavage with 3% Na(Hg) is remarkably mild, selective, and general to a variety of other p-phenylbenzoyl amides. Thus BPCO amides 11a,b (1.0 g) derived from morpholine and n-amylamine, respectively, react smoothly with 3% Na(Hg) (20 g) in MeOH (25°, 4 hr, N_2 atmosphere) to afford



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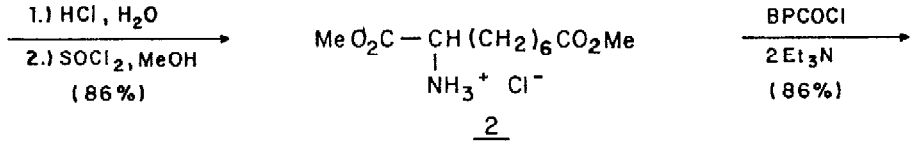

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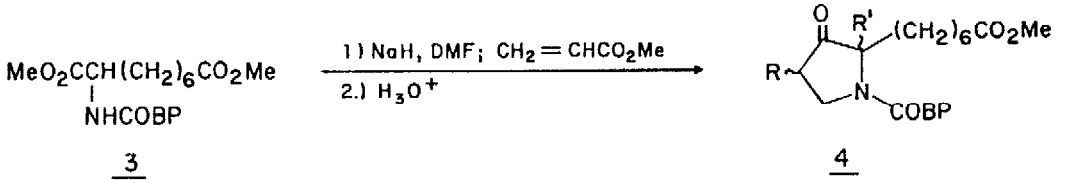

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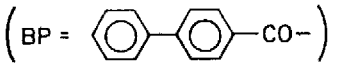
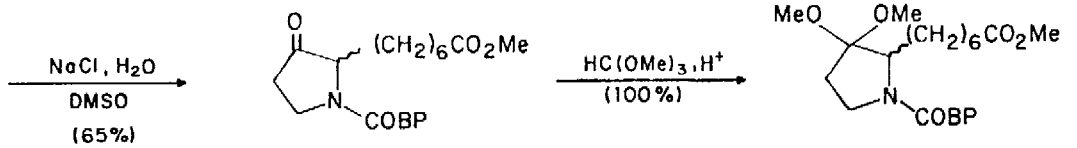
(BP =  CO−)

R = CO_2CH_3, R' = H (65%)
R = H, R' = CO_2CH_3 (35%)



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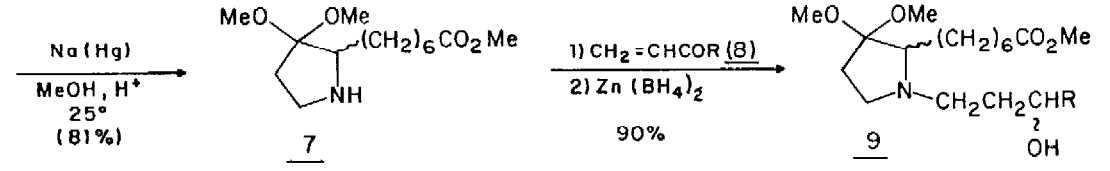

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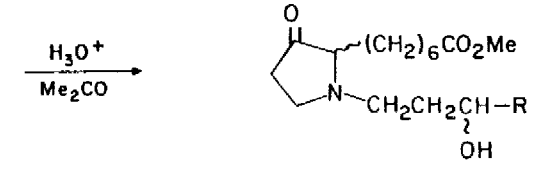

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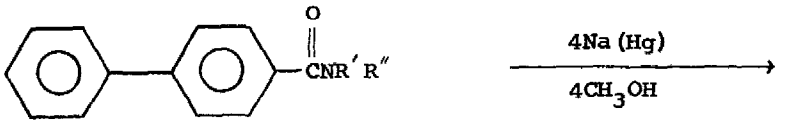
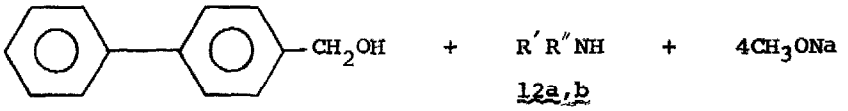
a R = nC_5H_{11}
b R = nC_7H_{15}
c R = $CH_2CH_2CF_3$

p-phenylbenzyl alcohol and the corresponding amines (12a,b) in 95-99% yield. The method further recommends itself as useful for the protection-deprotection of



11a,b



12a,b

(a: $R' = H$, $R'' = nC_5H_{11}$; b: $R',R'' = CH_2CH_2OCH_2CH_2$)

primary and secondary amines because BPCO derivatives of even liquid amines can be handled as crystalline solids.[9] Under the reaction conditions described AcOMe, and $CH_3(CH_2)_{10}CO_2CH_3$ are unchanged by 3% Na (Hg), and $C_6H_5CONMe_2$ reacts only very slowly.

Amine 7 underwent Michael addition to vinyl ketones, $RCOCH{=}CH_2$ (8a,b,c), to afford the corresponding amino ketones which, without isolation were reduced with $Zn(BH_4)_2$ in ether/glyme to the corresponding ketal amino alcohols 9a,b,c. Hydrolysis of the ketal groups of 9 with 1.1 equivalent of p-TsOH·H_2O in acetone (25°, 16 hr) gave the corresponding racemic azaprostanoids 10a,b,c as oils [ν_{max} 1752, 1737 cm^{-1}, pmr δ 4.50 (m, 1, COCHN), 3.65 (s, 3, OCH_3), 0.88 (t, 3, CCH_3; homogeneous by TLC on silica gel (1:1 $CHCl_3$-ether, iodine); HRMS m/e for M^+ agree within 10 ppm].

In vitro tests[10] on these 12-azaprostanoids indicate that the threshhold doses necessary to cause contractions of strips of rat fundus muscle are for 10a,b, and c about 100 ng, 50 ng, and 50 ng/ml, respectively. A dose-responsive curve plotted for 10a shows a slope factor and maximum response identical (within experimental error) with those measured for natural prostaglandin E_1. These compounds also stimulate rat uterus muscle.

Details will be published later.

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4. G. Bollinger and J. M. Muchowski, Tetrahedron Lett., 2931 (1975) and J. W. Bruin, H. de Konig, and H. Huisman, ibid., 4599 (1975), report the synthesis of 8-azaprostanoids.
5. Cf. M. Augustin, Chem. Ber. 99, 1040 (1966); Acta Chem. Acad. Sci Hung. 46, 85 (1965), Chem. Abst. 64: 1949 g.
6. A. P. Krapcho, Tetrahedron Lett., 1091 (1974); ibid 975 (1973).
7. Amino ketal 7 can be efficiently resolved as its crystalline d or ℓ-tartrate salts (m.p. 137-8°). However, this communication describes only the use of racemic 7 to produce prostanoids 10 as mixtures of diastereomers.
8. Electrochemically generated tetramethyl ammonium amalgam [L. Horner, Chem. Ber. 1715, 3462 (1965)] also cleaves BPCO amides. I am indebted to Dr. R. F Drury of this Department for suggesting that Na(Hg) might serve more conveniently.
9. Methyl p-phenylbenzoate is reductively cleaved by 3% Na(Hg), suggesting that the method may also be applicable to the selective cleavage of pphenylbenzoate esters in the presence of other esters.
10. I am indebted to Dr. W. F. Herblin of this Department for providing these biological data.