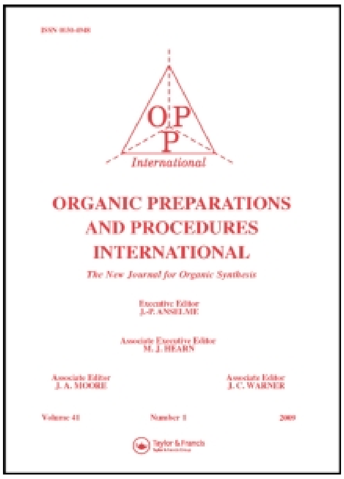


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

THE BECKMANN AND SCHMIDT REARRANGEMENTS OF 6-OXO-MORPHINE ALKALOIDS

R. Bognár[a]; S. Makleit[a]; L. Radics[b]; I. Seki[c]
[a] Institute of Organic Chemistry L. Kossuth University, Debrecen, Hungary [b] Central Chemical Research Institute Hungarian Academy of Sciences, Budapest, Hungary [c] Fermentation Res. Laboratories, Sankyo Co. Ltd., Tokyo, Japan

To cite this Article Bognár, R. , Makleit, S. , Radics, L. and Seki, I.(1973) 'THE BECKMANN AND SCHMIDT REARRANGEMENTS OF 6-OXO-MORPHINE ALKALOIDS', Organic Preparations and Procedures International, 5: 2, 49 — 54

To link to this Article: DOI: 10.1080/00304947309356465

URL: http://dx.doi.org/10.1080/00304947309356465

ORGANIC PREPARATIONS AND PROCEDURES INT. 5(2), 49-54 (1973)

THE BECKMANN AND SCHMIDT REARRANGEMENTS OF 6-OXO-MORPHINE ALKALOIDS

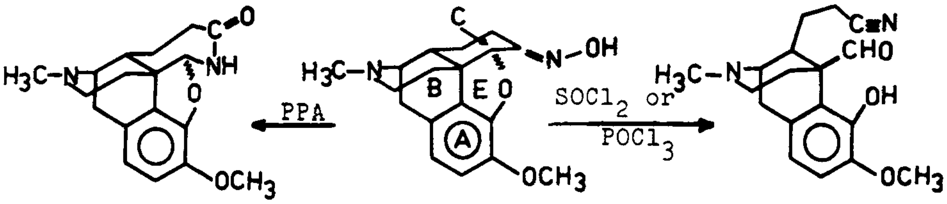
R. Bognár, S. Makleit, L. Radics* and I. Seki**

Institute of Organic Chemistry
L. Kossuth University, Debrecen 10, Hungary

*Central Chemical Research Institute
Hungarian Academy of Sciences, Budapest, Hungary

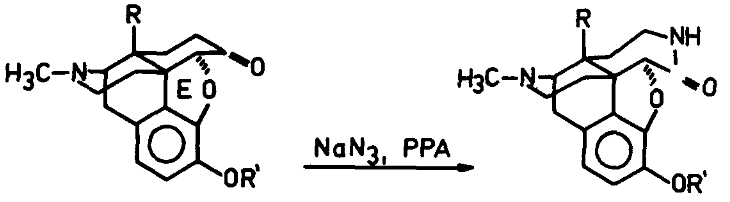
**Fermentation Res. Laboratories
Sankyo Co. Ltd. Shinagawa-ku, Tokyo, Japan

The Beckmann Rearrangement of dihydrocodeinone oxime (Ib) gave C-seco-aldehydonitrile[1] (II). In 1970, one of us[2] obtained a non-homogeneous amorphous product on treatment of Ib with polyphosphoric acid. This was shown to contain a component of lactam character by its IR spectrum.



III Ib II

Upon careful reexamination of this reaction, we have isolated from the amorphous substance a homogeneous crystalline compound, which on the basis of its IR and NMR spectra was determined to be C-homo-6-azadihydrocodeine-6a-one (III). On the other hand, the Schmidt reaction of dihydrocodeinone (Ia) produced the isomeric lactam, the structure of which was assigned by IR and NMR spectroscopy to be C-homo-6a-aza-dihydrocodeinone (IVa). Similarly, the Schmidt reaction of

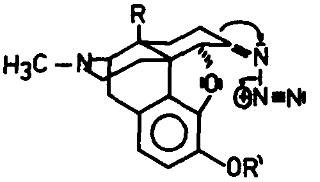


Ia: R=H, R'=CH_3
Ic: R=R'=H
Id: R=OH, R'=CH_3

IVa: R=H, R'=CH_3
IVb: R=R'=H
IVc: R=OH, R'=CH_3

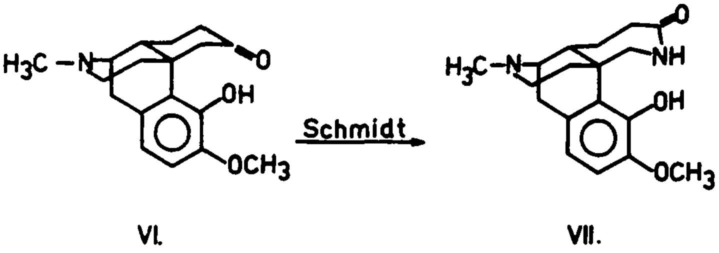
dihydromorphinone (Ic) and 14-hydroxy-dihydrocodeinone (Id) also gave the corresponding lactams IVb and IVc respectively. Methylation of IVb with methyl p-toluenesulfonate^2 gave IVa.

Since the structure of III indicates that the configuration of dihydrocodeinone oxime is as shown, ring expansion occurs with cleavage of the C_5-C_6 bond. In order to rationalize the formation of the main products of the Schmidt reaction of IVa-c, we consider that the diazoimine intermediate assumes a position under the plane of the C ring, this geometry being determined by interaction with the oxygen atom of the ether in the dihydrofuran ring E. In order to verify this hypoth-



Va: R=H, R'=CH_3
Vb: R=R'=H
Vc: R=OH, R'=CH_3

esis, the Schmidt reaction of dihydrothebainone with opened ether bridge (VI), was studied. As expected, the product was the C-homo-6-aza-6a-ketone (VII), identical to the compound previously obtained from the Beckmann rearrangement of dihydrothebainone oxime.[2]



EXPERIMENTAL[3]

C-Homo-6-azadihydrocodeine-6a-one (III). - It was prepared as previously described.[2] The resulting amorphous product was crystallized twice from benzene-petroleum ether to give 0.75 g. (24%) of colorless solid, mp. 188-190°; $[\alpha]_D$ = -264.9° (0.268, chloroform).

R_f: 0.710 (chloroform:methanol = 9.5:0.5; Eastman Chromagram No. 6062, Al_2O_3).

R_f: 0.509 (chloroform:acetone:methanol = 4:2:0.5; Eastman Chromagram No. 6062, Al_2O_3). The developing agent was iodine. NMR: C_5H 5.26 pp,. M–H 7.36 ppm, $J_{5,NH}$ 8-8.5 Hz. N–H (d) exchangeable with D_2O, C_5-H (d) changes to a singlet upon exchange with D_2O.

C-Homo-6a-azadihydrocodeinone (IVa). - One gram (0.0033 mole) of dihydrocodeinone was heated in 300 g. of polyphosphoric acid in the presence of 0.3 g. sodium azide (0.0046 mole) at 65° for 10 hrs. The reaction mixture was then poured on ice water, basified with conc. ammonium hydroxide and extracted with three 30 ml. portions of chloroform. The combined organic extracts were washed with two 10 ml. portions of water, dried over magnesium sulfate and evaporated to dryness. Recrystallization from benzene-petroleum ether yielded 0.55 g. (52%), mp. 179-180°; $[\alpha]_D$ = -177.7° (0.45, chloroform).

Anal. Calcd. for $C_{18}H_{22}O_3N_2$: N, 8.91. Found: N, 9.33.
MW: 314; MW: 314 (mass. spec.)

R_f: (under conditions given for III) 0.654 and 0.437, resp. The NMR spectrum showed the NH around δ 6.9 as a multiplet. On addition of D_2O, or irradiation of the NH, the doublet of C_5-H at δ 4.87 changed into singlet and the multiplet structure appearing at 2.75 ppm changed also. Upon irradiation of the C_5-H signal, the NH resonance changed to a triplet. The sum of the coupling constants (14 Hz) indicates that the two protons causing the triplet structure occupy vicinal positions with respect to the NH group. The chemical shift of these two protons (δ 2.75) corresponds to values characteristic of the CH_2 adjacent to an amide NH. The splitting of the C_5-H doublet is about 1.8 Hz.

IR: 3210, 3100 cm^{-1} amide (NH), amide I 1678 cm^{-1}, amide III 1292 cm^{-1}.

C-Homo-6a-azadihydromorphinone (IVb). - Prepared as described for IVa from 5.0 g. of dihydromorphinone, but the extraction was performed with a 2:1 chloroform-ethanol mixture; yield:

2.1 g. (40%), mp. 235-236° from acetone; $[\alpha]_D$ = -189.8° (0.474, abs. ethanol).

Anal. Calcd. for $C_{17}H_{20}O_3N_2$: N, 9.33. Found: N, 9.87. Methylation[2] gave a product which is identical to IVa.

C-Homo-6a-aza-14-hydrox-dihydrocodeinone (IVc). - 14-Hydroxydihydrocodeinone 5.5 g. (0.0175 mole) was dissolved in 165 g. of polyphosporic acid at 65° and allowed to stand for 10 hrs. at 65° in the presence of 1.65 g. (0.025 mole) of sodium azide. The mixture was stirred for 2 hrs. poured into 400 ml. of ice water basified with conc. ammonium hydroxide and extracted with three 150 ml. portions of chloroform. The combined extracts were washed with two 30 ml. portions of water, dried over magnesium sulfate and evaporated to give 2.53 g. of an oil which when rubbed with 10 ml. of hot benzene yielded 1.37 g. (23.4%) of crystals, mp. 215°, homogeneous by thin layer chromatography benzene-methanol = 8:2; silica gel-G; Dragendorff. $[\alpha]_D$ = -196° (0.51, chloroform).

Anal. Calcd. for $C_{18}H_{22}N_2O_4$: N, 8.48. Found: N, 8.05. NMR: C_5H doublet at δ 4.82, $J_{5,NH}$ 1.9 Hz.

C-Homo-6-aza-dihydrothebaine-6a-on (VII). - Obtained from dihydrothebainone oxime,[2] crystallized from benzene-petroleum ether.

$[\alpha]_D$ = +20.8° (0.42, chloroform), mp., IR, NMR spectra identical with the literature values.[2]

It was also prepared from 1.0 g. 0.00317 mole of dihydrothebainone by heating in 30 g. of polyphosphoric acid with

0.3 g. (0.00461 mole) of sodium azide as described for IVa. Crystallization from abs. ether yielded 160 ml. (16%) of product whose mp., optical rotation, IR, NMR are identical with those of the product obtained by the first procedure.

REFERENCES

1. C. Schöpf, Ann. 452, 211 (1927).

2. I. Seki, Chem. Pharm. Bull. 18/6, 1269 (1970).

3. NMR spectra were determined on a Varian 100 MHz spectrometer in $CDCl_3$ and are reported in δ values using TMS as an internal standard. The IR spectra were obtained as KBr pellet on a UR 10 W spectrometer.

(Received December 26, 1972; in revised form April 13, 1973)