Chemistry of Natural Compounds, Vol. 39, No. 1, 2003

BECKMANN REARRANGEMENT OF DIMETHYLCYCLOPENTANONEPIMARATE OXIME

E. V. Tret′yakova, O. B. Flekhter, F. Z. Galin,
I. P. Baikova, and G. A. Tolstikov

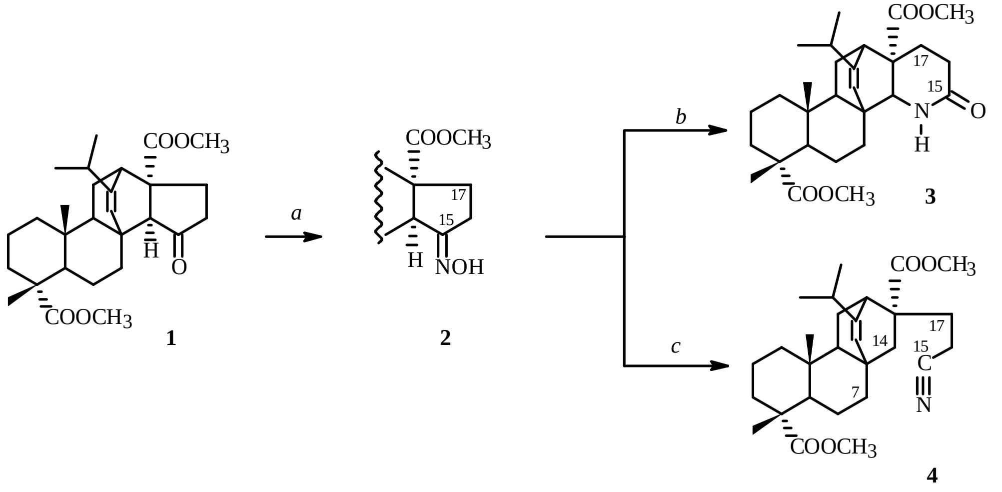
UDC 547.824:542.91:548.737

*Beckmann rearrangement of dimethylcyclopentanonepimarate-15-oxime **2** was used to produce lactam **3** or seco-nitrile **4**, depending on the conditions. The structures of the synthesized compounds were confirmed by IR and NMR spectroscopies.*

Key words: dimethylcyclopentanonepimarate, Beckmann rearrangement, lactam, nitrile.

The Beckmann rearrangement is a convenient method for producing amides and nitriles, which are used as intermediates in the preparation of pharmacologically active azacyclic compounds.

In continuation of studies [1, 2] on the synthesis of novel N-containing diterpenoids, we investigated the Beckmann rearrangement of 15-hydroxyimino-18-isopropyl-4,10-dimethyl-4,13-dimethoxycarbonyl-8,12-ethenocyclopentanoperhydrophenanthrene **2** (dimethylcyclopentanonepimarate oxime), which was prepared from diterpene ketone **1** by the literature method [3] of reaction with hydroxylamine hydrochloride in ethanol in 75% yield after recrystallization. Oxime **2** reacted with thionyl chloride in absolute dioxane [4] to form a single product (TLC monitoring), the structure of which corresponded to lactam **3** (86% yield). The IR spectrum of **3** contains a strong band at 1640-1670 cm^{-1} that is characteristic of amide carbonyl and bands at 1540 and 3230-3240 cm^{-1} that correspond to N–H deformations and stretchings. The N–H proton appears in the PMR spectrum at δ 5.65 ppm as a broad signal. The signal for C-15 in the ^{13}C NMR is shifted (δ 176.0 ppm) compared with that of starting **2** (δ 166.9 ppm). The signal for H-16 (δ 2.20-2.32 ppm) in the PMR spectrum is found at stronger field compared with that of **2** (δ 2.61-2.82 ppm).



a. $NH_2OH \cdot HCl$, EtOH; *b*. $SOCl_2$, dioxane; *c*. TsCl, 0 ° C, pyridine

However, **2** reacted with tosyl chloride in pyridine [2] through a second-order Beckmann rearrangement to give quantitatively seco-nitrile **4**. The IR spectrum of **4** exhibits a CN band at 2245-2250 cm^{-1}. The signal for C-15 in the ^{13}C NMR spectrum appears at δ 112.5 ppm; for H-14 in the PMR spectrum, at δ 2.56-2.66 ppm as a multiplet, in contrast with that of **2** (δ 2.95 ppm as a broad signal).

Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences, 450054 Ufa, pr. Oktyabrya, 71, fax (3472) 35 60 66, e-mail: obf@anrb.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 15-16, January-February, 2003. Original article submitted February 18, 2003.

0009-3130/03/3901-0016$25.00 ©2003 Plenum Publishing Corporation

EXPERIMENTAL

IR spectra were recorded on Specord M80 and UR-20 spectrometers in mineral oil; ^{13}C NMR and PMR on a Bruker AM-300 spectrometer (75.5 and 300 MHz, respectively) in $CDCl_3$ with TMS internal standard. Melting points were determined on a Boetius microstage.

TLC analysis was performed on Silufol (Chemapol, Czech Rep.) plates using $CHCl_3$:CH_3OH (20:1). Compounds were developed by phosphotungstic acid solution (10%) in ethanol with subsequent heating at 100-120°C for 2-3 min. Dimethylcyclopentanonepimarate **1** was prepared as before [5].

Elemental analyses agreed with those calculated.

15-Hydroxyimino-18-isopropyl-4,10-dimethyl-4,13-dimethoxycarbonyl-8,12-ethenocyclopentanoperhydrophenanthrene (2). Dimethylcyclopentanonepimarate (**1**, 1 mmole, 0.47 g) in ethanol (10 mL) was treated with $NH_2OH\cdot HCl$ (0.5 g) in $CHCl_3$ (5 mL), boiled for 8 h, treated with cold water (50 mL), and extracted with $CHCl_3$ (3×30 mL). The combined extracts were washed with water (3×30 mL), dried over $MgSO_4$, and evaporated in vacuum. The solid was recrystallized from EtOH. Yield 0.35 g (75%), mp 108-110°C. IR spectrum (ν, cm^{-1}): 720, 755, 860, 1070, 1190, 1210, 1250, 1380, 1460, 1560, 1620, 1730, 3370.

PMR spectrum (δ, ppm, J/Hz): 0.51 (s, 3H, 23-H), 0.80 (d, J = 6.8, 3H, 21-H/22-H), 0.85 (d, J = 6.8, 3H, 22-H/21-H), 0.89-0.98 (m, 2H, 1-H_a, 11-H_a), 1.05 (s, 3H, 24-H), 1.19-1.55 (m, 8H, 1-H_e, 2-$H_{a,e}$, 3-H_e, 6-$H_{a,e}$, 7-$H_{a,e}$), 1.57-1.78 (m, 4H, 3-H_a, 11-H_e, 9-H, 5-H), 2.25 (ddd, 1H, $^4J_{12,19}$ = 1.6, $^3J_{12,11a}$ = 2.2, $^3J_{12,11b}$ = 13.2, 12-H), 2.35 (sept., 1H, J = 6.8, 20-H), 2.61-2.82 (m, 4H, 16-$H_{a,e}$, 17-$H_{a,e}$), 2.95 (br.s, 1H, 14-H), 3.55 (s, 3H, 28-H), 3.65 (s, 3H, 27-H), 5.41 (br.s, 1H, 19-H), 8.62 (br.s, 1H, NOH).

^{13}C NMR spectrum: 37.5 (C-1), 17.1 (C-2), 35.4 (C-3), 47.2 (C-4), 51.9 (C-5), 21.9 (C-6), 34.2 (C-7), 41.1 (C-8), 52.2 (C-9), 36.6 (C-10), 25.9 (C-11), 37.9 (C-12), 57.8 (C-13), 52.8 (C-14), 166.9 (C-15), 27.6 (C-16), 42.3 (C-17), 146.5 (C-18), 126.3 (C-19), 34.0 (C-20), 20.9 (C-21), 20.1 (C-22), 16.8 (C-23), 15.5 (C-24), 179.3 (C-25), 177.2 (C-26), 49.3 (C-27), 56.5 (C-28).

15-Oxo-15-aza-*E*-homo-18-isopropyl-4,10-dimethyl-4,13-dimethoxycarbonyl-8,12-ethenocyclopentanoperhydrophenanthrene (3). A solution of **2** (1 mmole, 0.47 g) in absolute dioxane (25 mL) was cooled to 10°C and treated with freshly distilled $SOCl_2$ (1 mL). The temperature was adjusted to ambient. The solution was treated with cold aqueous KOH solution (50 mL, 1%). The precipitate was filtered off, washed with water, dried, and recrystallized from ethanol. Yield 0.37 g (78%), mp 118-120°C. IR spectrum (ν, cm^{-1}): 770, 827, 860, 890, 920, 1010, 1045, 1072, 1098, 1129, 1156, 1210, 1260, 1375, 1470, 1610, 1640-1670, 1730, 3230-3240.

PMR spectrum (δ, ppm, J/Hz): 0.60 (s, 3H, 23-H), 0.89-0.98 (m, 2H, 1-H_a, 11-H_a), 0.99 (d, J = 6.8, 3H, 21-H/22-H), 1.03 (d, J = 6.8, 3H, 22-H/21-H), 1.05 (s, 3H, 24-H), 1.19-1.55 (m, 8H, 1-H_e, 2-$H_{a,e}$, 3-H_e, 6-$H_{a,e}$, 7-$H_{a,e}$), 1.57-1.78 (m, 4H, 3-H_a, 11-H_e, 9-H, 5-H), 1.85-1.98 (m, 2H, 17-$H_{a,e}$), 2.08 (ddd, 1H, $^4J_{12,19}$ = 1.6, $^3J_{12,11a}$ = 2.2, $^3J_{12,11b}$ = 13.2, 12-H), 2.15 (sept., 1-H, J = 6.8, 20-H), 2.20-2.32 (m, 2H, 16-$H_{a,e}$), 2.80 (br.s, 1H, 14-H), 3.65 (s, 3H, 28-H), 3.80 (s, 3H, 27-H), 5.40 (br.s, 1H, 19-H), 5.65 (br.s, 1H, NH).

^{13}C NMR spectrum: 37.8 (C-1), 16.9 (C-2), 36.7 (C-3), 46.9 (C-4), 51.4 (C-5), 21.8 (C-6), 33.8 (C-7), 42.1 (C-8), 51.9 (C-9), 37.1 (C-10), 25.3 (C-11), 41.8 (C-12), 6.25 (C-13), 52.4 (C-14), 176.0 (C-15), 29.1 (C-16), 43.7 (C-17), 147.5 (C-18), 123.6 (C-19), 33.2 (C-20), 20.7 (C-21), 19.8 (C-22), 16.7 (C-23), 15.7 (C-24), 179.0 (C-25), 173.7 (C-26), 49.2 (C-27), 52.6 (C-28).

14,15-Seco-15-nitrilo-18-isopropyl-4,10-dimethyl-4,13-dimethoxycarbonyl-8,12-ethenocyclopentanoperhydrophenanthrene (4). A solution of **2** (1 mmole, 0.47 g) in dry pyridine (10 mL) at 0°C was treated with TsCl (5.25 mmole, 1.00 g) in pyridine (5 mL). The mixture was stirred for 5 h at 5°C, left for 40 h at room temperature, and treated with cold HCl solution (50 mL, 5%). The precipitate was filtered off, washed with water, dried, and purified analogously to **3**. Yield 0.33 g (72%), mp 125-127°C. IR spectrum (ν, cm^{-1}): 770, 827, 860, 890, 920, 1010, 1045, 1072, 1098, 1129, 1156, 1210, 1260, 1375, 1470, 1730, 2245-2250.

PMR spectrum (δ, ppm, J/Hz): 0.48 (s, 3H, 23-H), 0.78-0.88 (m, 2H, 1-H_a, 11-H_a), 0.91 (d, J = 6.8, 3H, 21-H/22-H), 1.00 (d, J = 6.8, 3H, 22-H/21-H), 1.05 (s, 3H, 24-H), 1.15-1.50 (m, 8H, 1-H_e, 2-$H_{a,e}$, 3-H_e, 6-$H_{a,e}$, 7-$H_{a,e}$), 1.55-1.75 (m, 4H, 3-H_a, 11-H_e, 9-H, 5-H), 2.09-2.15 (m, 2H, 17-$H_{a,e}$), 2.21 (sept., 1-H, J = 6.8, 20-H), 2.42 (ddd, 1H, $^4J_{12,19}$ = 1.6, $^3J_{12,11a}$ = 2.2, $^3J_{12,11b}$ = 13.2, 12-H), 2.56-2.66 (m, 4H, 14-$H_{a,e}$, 16-$H_{a,e}$), 3.66 (s, 3H, 28-H), 3.80 (s, 3H, 27-H), 5.29 (br.s, 1H, 19-H).

^{13}C NMR spectrum: 37.6 (C-1), 16.9 (C-2), 36.7 (C-3), 47.5 (C-4), 51.9 (C-5), 21.7 (C-6), 33.3 (C-7), 42.1 (C-8), 52.2 (C-9), 37.1 (C-10), 25.5 (C-11), 40.5 (C-12), 65.5 (C-13), 55.2 (C-14), 112.5 (C-15), 29.8 (C-16), 46.0 (C-17), 147.3 (C-18), 126.0 (C-19), 33.0 (C-20), 20.6 (C-21), 19.9 (C-22), 16.7 (C-23), 15.7 (C-24), 179.1 (C-25), 176.9 (C-26), 51.1 (C-27), 57.6 (C-28).

REFERENCES

1. O. B. Flekhter, E. V. Tret′yakova, F. Z. Galin, L. T. Karachurina, L. V. Spirikhin, F. S. Zarudii, and G. A. Tolstikov, *Khim.-Farm. Zh.*, **36**, No. 8, 29 (2002).
2. E. V. Tret′yakova, O. B. Flekhter, F. Z. Galin, L. V. Spirikhin, and G. A. Tolstikov, *Khim. Prir. Soedin.*, 206 (2002).
3. Weigand-Hilgetag, *Organisch-Chemische Experimentierkunst*, Verlag, Leipzig (1964).
4. G. A. Tolstikov, Kh. A. Alibaeva, and M. I. Goryaev, *Zh. Org. Khim.*, **5**, 1625 (1969).
5. W. Herz, R. C. Blackstone, and M. G. Nair, *J.Org. Chem.*, **32**, No. 10, 2992 (1967).