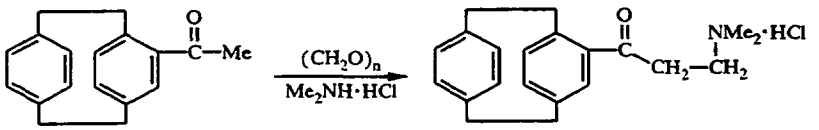
Chemistry of Heterocyclic Compounds, Vol. 33, No. 8, 1997

SYNTHESIS, STRUCTURE, AND BIOLOGICAL ACTIVITY OF [2.2]PARACYCLOPHANES. 7.* SYNTHESIS OF 2-([2.2]PARACYCLOPHAN-4-YL)PYRIDINES, -TETRAHYDROQUINOLINES, AND -BENZO[*h*]QUINOLINES BASED ON CONDENSATION OF 4-(β-DIMETHYLAMINOPROPIONYL)[2.2]PARACYCLOPHANE WITH PRIMARY AMINES

L. I. Kryvenko, S. A. Soldatova, O. V. Zvolinskii, É. É. Romanenko, M. I. Struchkova, and A. T. Soldatenkov

Condensation of 4-(β-dimethylaminopropionyl)paracyclophane with aliphatic aldehydes or cyclohexanones in the presence of hydroxylamine gave 2-([2.2]paracyclophan-4-yl)pyridines and -5,6,7,8-tetrahydroquinolines respectively. Reaction of these salts with α-naphthylamine gives a mixture of paracyclophanyl substituted 1,2,3,4-tetrahydrobeno[h]quinoline and benzo[h]quinoline.

We have previously reported [2] the synthesis of [2.2]paracyclophanes containing γ-pyridyl or γ-tetrahydropyridyl fragments at the C_4 atom. In this paper we report the synthesis of a series of pyridines, tetrahydroquinolines and tetrahydrobenzo[*h*]quinolines having a paracyclophane substituent in position 2 of the heterocycle. The starting material for these syntheses was 4-(β-dimethylaminopropionyl)paracyclophane hydrochloride (II), which is a Mannich salt obtained by condensation of 4-acetylparacyclophane (I) with paraformaldehyde and dimethylamine hydrochloride.



I II

Condensation of salt II with aliphatic (propionic or butyric) aldehydes and hydroxylamine by method [3-5] gave 5-alkyl-2-([2.2]paracyclophan-4-yl)pyridines III and IV. A similar condensation of cyclohexanone gives 5,6,7,8-tetrahydro-2-([2.2]paracyclophan-4-yl)quinolines V and VI.

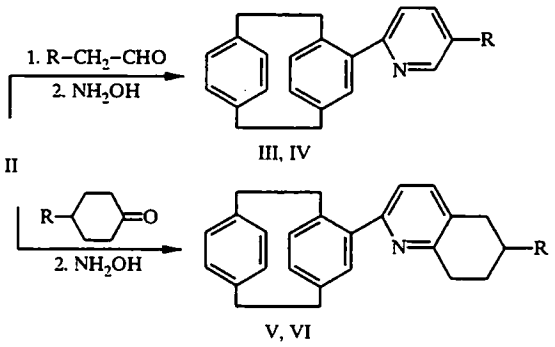
The presence of the pyridine ring is indicated in the PMR spectra of III and IV by a broadened singlet for the α-proton at 8.5 ppm. The β- and γ-protons give doublet (J = 8 Hz) and double doublet (J = 8 and 1.8 Hz) signals at 7.3 and 7.5 Hz respectively. In the PMR spectra of V and VI the pyridine β- and γ-protons occur at 7.3 and 7.48 ppm respectively as doublet signals with spin-spin coupling of 8 Hz.

*For Communication 6, see [1].

Russian University of National Friendship, Moscow 117198. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1069-1073, August, 1997. Original article submitted May 6, 1997.

0009-3122/97/3308-0933$18.00

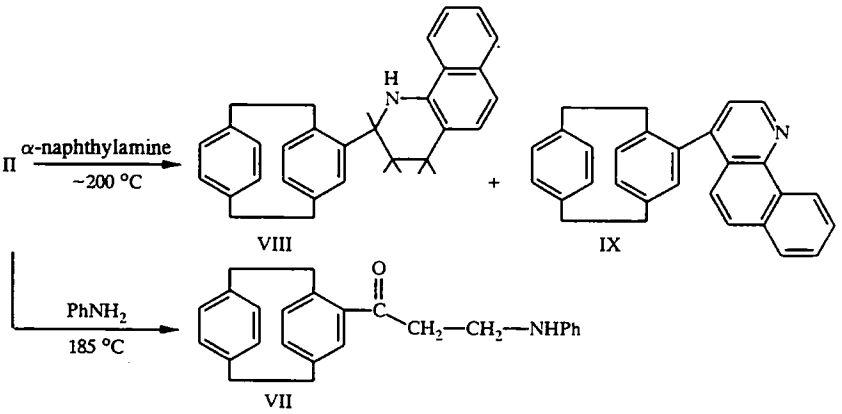
The mass spectra of III-VI shows both molecular ion peaks (basically with low or moderate intensity) together with high intensity peaks for para-xylene (m/z 104) and ion $[M-104],^{+\cdot}$ typical for fragmentation of mono substituted [2.2]paracyclophanes under electron impact.



III R = Me; IV R = Et; V R = H; VI R = C_6H_{10}–Pr

A modification of the Bischler method for preparing 2-substituted indoles was proposed in [6] and was based on condensation of (2-R-2-oxoethyl)trimethyl)trimethylammonium bromide with aniline. Using this method for preparing the indole system, we have studied the potential synthesis of quinolines and benzo[*h*]quinolines by condensation of 4-(β-dimethylaminopropionyl)paracyclophane II with aniline and α-naphthylamine. The reaction with aniline gave not the expected quinoline but a 49% yield of the transamination product 1-oxo-1-(paracyclophan-4-yl)-3-phenylaminopropane (VII). The reaction of salt II with naphthylamine gave low yields of two cyclocondensation products which were 2-([2.2]cyclophan-4-yl)-1,2,3,4-tetrahydrobenzo[*h*]quinoline (VIII) and 4-([2.2]paracyclophan-4-yl)benzo[*h*]quinoline (IX).

Formation of the 2-substituted benzoquinoline VIII evidently occurs via an intermediate Schiff base [6]. As regards the 4-substituted benzoquinoline IX, it might be expected that its formation would include a transamination stage and this is indirectly confirmed by the formation of the phenylaminopropane VII in the case of attempted cyclocondensation of salt II with aniline.



The IR spectrum of VIII shows NH absorption bands at 3440 cm^{-1}. In its PMR spectrum there are signals for the paracyclophane aromatic protons at 5.7-6.7 ppm, and for the naphthyl fragment as a complex multiplet at 7.35-7.58 ppm integrating to four proton units for 7-, 8-, 9-, and 10-H. Two doublets at 7.73 and 7.9 ppm, each integrating to one proton and with a spin-spin coupling of 7.7 Hz, are assigned to 6-H and 5-H respectively. The four protons of the two tetrahydropyridine CH_2 groups occur as a complex multiplet at 1.95-2.8 ppm, and the methine 2-H proton as a multiplet at 3.6 ppm. The NH proton is found as a broadened singlet at 4.33 ppm.

The PMR spectrum of IX has a different character. Formation of the aromatic pyridine fragment is confirmed by the presence of a doublet signal with spin-spin coupling 4.6 Hz at 9.23 ppm and a broadened doublet with the same coupling at 7.86 ppm, which are assigned to the α- and β-protons respectively. A broadened doublet at 9.45 ppm with J = 7.7 Hz is observed for the naphthyl 10-H proton, experiencing a strong deshielding by the neighboring heteroatom.

EXPERIMENTAL

PMR spectra for the compounds synthesized were taken on a Bruker spectrometer at 80 and 200 MHz using $CDCl_3$ solvent and TMS internal standard. IR spectra were recorded on a Specord IR-75 for KBr tablets. Mass spectra were obtained on an MK-1303 with an ionization energy of 70 eV. The course of the reaction and the purities of the obtained products were monitored by TLC on Silufol UV-254 plates.

4-(β-Dimethylaminopropionyl)-[2.2]paracyclophane (II). The reaction mixture obtained from 4-acetyl[2.2]paracyclophane (*I*, 10 g, 40 mmole), paraformaldehyde (2 g, 66 mmole), dimethylamine hydrochloride (3.08 g, 40 mmole), 2-propanol (30 ml), and a catalytic amount of conc. HCl was refluxed for 10 h, cooled to 20°C, and the salt II precipitated from isopropanol using heptane. The precipitate was filtered and dried to give salt II (11.37 g, 83%) as white crystals with mp 162-163°C. Found, %: C 73.37; H 7.56; Cl 10.21; N 4.29. $C_{21}H_{26}ClNO$. Calculated, %: C 73.36; H 7.57; Cl 10.33; N 4.08. M 343.5. IR spectrum: 1679 (C=O); 2650 (s) [$-N(CH_3)_2$]. PMR spectrum: 7.03 (1H, br.s, 5-H); 6.3-6.8 (6H, m, H_{arom}); 2.7-3.9 (12H, m, CH_2); 2.8 ppm (6H, s, 2 CH_3). ^{13}C NMR spectrum: 197.4 (C=O); 141.9; 140.4; 139.9; 139.4 and 136.1 (C_{quat}); 137.3; 136.5; 133.7; 133.0; 132.8; 132.2 and 131.1 (CH_{arom}); 53.1; 35.9; 35.3; 35.0; 34.9 and 34.7 (CH_2); 43.4 ppm (CH_3).

Cyclocondensation of Salt II with Aliphatic Aldehydes or Cyclohexanone in the Presence of Hydroxylamine. General method. A mixture of salt II (5.8 mmole), dioxane (25 ml), and the corresponding aldehyde or cyclohexanone (7 mmole); sodium acetate (0.7 mmole), and hydroquinone (0.01 g) was stirred for 6 h at 100-102°C. The reaction mixture was cooled to 40°C and hydroxylamine hydrochloride (17 mmole) and water (5 ml) were added with stirring, and stirring was continued for a further 10 h at 90-92°C. At the end of the reaction (TLC monitoring), dioxane (15 ml) was distilled off, the reaction mixture was cooled to 20°C, and aqueous NaOH (20%) was added with stirring to pH 8. The organic layer was separated, dissolved in hot toluene, and purified from tarry materials on the filter with a small layer of Al_2O_3. Solvent was evaporated and the residue was chromatographed on an Al_2O_3 column (h = 30 cm, d = 2 cm, eluent ethyl acetate–hexane, 1:30).

2-([2.2]Paracyclophan-4-yl)-5-methylpyridine (III) was obtained from propanal (0.4 g) in a 0.26 g (15%) yield as colorless crystals with mp 132-135°C and R_f 0.45 (pentane–ethyl acetate, 2:1): Found, %: C 87.83; H 6.97; N 4.39. $C_{22}H_{21}N$. Calculated, %: C 88.29; H 7.02; N 4.68. M 299. Mass spectrum, m/z (%): M 299 (18), $[M-104]^{+\cdot}$ 195 (100), 104 (31). PMR spectrum pyridine ring: 8.5 (1H, br.s, 6-H); 7.55 (1H, dd, J = 8 and 1.8 Hz, 4-H); 7.3 (1H, d, J = 8 Hz, 3-H); paracyclophane ring: 6.75 (1H, br.s, 5-H); 6.4 (6H, m, H_{arom}); 3.6 (1H, m, 2-H); 2.9 (7H, m, H_{aliph}); 2.4 ppm (3H, s, CH_3).

2-([2.2]Paracyclophan-4-yl)-5-ethylpyridine (IV) was obtained from butanal (0.5 g) in a 0.46 g (25%) yield as colorless crystals with mp 58-64°C and R_f 0.51 (pentane–ethyl acetate, 2:1). Found, %: C 87.82; H 7.24; N 4.38. $C_{23}H_{23}N$. Calculated, %: C 88.18; H 7.35; N 4.47. M 313. Mass spectrum, m/z (%): M^+ 313 (38), $[M-104]^{+\cdot}$ 209 (100), 104 (63). PMR spectrum pyridine ring: 8.5 (1H, br.s, 6-H); 7.5 (1H, dd, J = 8 and 1.8 Hz, 4-H); 7.3 (1H, d, J = 8 Hz, 3-H); paracyclophane ring: 6.75 (1H, br.s, 5-H); 6.4 (6H, m, H_{arom}), 3.6 (1H, m, 2-H); 3.0 (7H, m, H_{aliph}), 2.7 (2H, q, $\underline{CH_2}CH_3$); 1.25 ppm (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$).

2-([2.2]Paracyclophan-4-yl)-5,6,7,8-tetrahydroquinoline (V) was prepared from cyclohexanone (0.7 g) in 0.35 g (18%) yield as a yellow oil with R_f 0.53 (heptane–ethyl acetate, 2:1). Found, % C 87.9; H 7.10; N 3.97. $C_{25}H_{25}N$. Calculated, %: C 88.5; H 7.37; N 4.13. M 339. Mass spectrum, m/z (%): 275 (7) $[M-104]^+$, 235 (90), 146 (64), 104 (100). PMR spectrum tetrahydroquinoline ring: 7.48 (1H, d, J = 8 Hz, 4-H); 7.3 (1H, d, J = 8 Hz, 3-H); 1.6 (8H, m, CH_2); paracyclophane ring: 6.93 (1H, br.s, 5-H); 6.5 (6H, m, H_{arom}); 3.96 (1H, m, 2-H); 3.0 ppm (7H, m, CH_2).

2-([2.2]Paracyclophan-4-yl)-6-(propylcyclohexyl)-5,6,7,8-tetrahydroquinoline (VI) was prepared from 4-(4-propylcyclohexyl)cyclohexanone (0.98 g) in 1 g (40%) yield as pale yellow crystals with mp 110-124°C and R_f 0.67 (heptane–ethyl acetate, 2:1). Found, %: C 87.92; H 8.53; N 3.41. $C_{34}H_{41}N$. Calculated, %: C 88.12; H 8.86; N 3.02. M 463. Mass spectrum, m/z %): M–463 (100), $[M-104]^{+\cdot}$ 359 (80), $[M-C_6H_{10}-Pr]^{+\cdot}$ 338 (6), 104 (19). PMR spectrum tetrahydroquinoline ring: 7.48 (1H, d, J = 8 Hz, 4-H); 7.3 (1H, d, J = 8 Hz, 3-H); 1.8 (24 H, m, H_{aliph}); paracyclophane ring: 6.65 (1H, br.s, 5-H); 6.4 (6H, m, H_{arom}); 3.8 (1H, m, 2-H); 3.0 ppm (7H, m, CH_2).

Condensation of Salt II with Aniline. A mixture of salt II (0.5 g, 1.5 mmole) and aniline (3 ml) was refluxed for 3 h. The product was cooled and treated with dilute HCl (1:4). The precipitate was filtered, washed with water, dried, and recrystallized from ethanol to give 1-oxo-1-([2.2]paracyclophan-4-yl)-3-phenylaminopropane (VII, 0.25 g, 49%) as beige crystals with mp 112-115°C and R_f 0.39 (chloroform). Found, %: N 4.31. $C_{25}H_{25}NO$. Calculated, %: N 3.94. M 355. IR

spectrum: 3370 (N−H), 1650 cm^{-1} (C=O). Mass spectrum, m/z (%): M^+ 355 (10), $[M-PhNH_2]^{+\cdot} = \Phi_1$ 262 (25), 250 (10), $[\Phi_1-104]^{+\cdot}$ 158 (40), 157 (28), 129 (18), 115 (18), 107 (58), 105 (23), 104 (90), 93 (100), 77 (25). PMR spectrum: 7.3 (2H, t, J = 7.8 Hz, o,o'-H aniline ring); 6.6 (10H, m, H_{arom}); 4.02 (2H, br.s, 2-H + NH); 3.6 (2H, br.s, O=C−CH_2); 2.6 ppm (10H, m, H_{aliph}). ^{13}C NMR spectrum: 201.5 (C=O); 137.3-147.7 (6 × C_{quat}); 129.3-136.4 (9 × CH); 113.0 and 117.5 (3 × CH); 34.9-39.3 ppm (6 × CH_2).

Condensation of Salt II with α-Naphthylamine. α-Naphthylamine (1.24 g, 8.7 mmole) and 2-3 drops of conc. HCl were added to salt II (1 g, 2.9 mmole). The reaction was carried out with stirring in molten naphthylamine at 200°C for 8 h. The product was cooled to 20°C and treated with dilute HCl (1:4). The precipitate was filtered, washed with water, dried, and separated on a silica gel column using hexane eluent. First eluted was 2-([2.2]paracyclophan-4-yl)benzo[*h*]-1,2,3,4-tetrahydroquinoline (VIII, 0.2 g, 18%) as light grey crystals with mp 218-220°C and R_f 0.88 (chloroform). Found, %: C 89.47; H 6.93; N 3.57. $C_{29}H_{27}N$. Calculated, %: C 89.46; H 6.94; N 3.6. M 389. IR spectrum: 3440 cm^{-1} (N−H). Mass spectrum, m/z (%): M^+ 389 (100), $[M-104]^{+\cdot}$ 285 (51), 180 (44), 104 (35). PMR spectrum benzoquinoline ring: 7.9 and 7.73 (each 1H, both d, J = 7.7 Hz, 5- and 6-H); 7.5 (4H, m, 7-, 8-, 9-, 10-H); 4.33 (1H, br.s, NH); 3.6 (1H, m, 2-H); 2.4 (4H, m, 3-, 4-H); paracyclophane ring: 7.00 (1H, d, J = 7 Hz, 7-H); 6.5 (5H, m, H_{arom}); 5.7 (1H, s, 5-H); 3.1 ppm (7H, m, H_{aliph}).

Next eluted was 4-([2.2]paracyclophan-4-yl)benzo[*h*]quinoline (IX, 0.06 g, 5%) as pink crystals with mp 170-172°C. Found, %: C 90.70; H 6.18; N 3.7. $C_{29}H_{23}N$. Calculated, %: C 90.39; H 5.97; N 3.64. M 385. PMR spectrum benzoquinoline ring: 9.45 (1H, br d, J = 7.7 Hz, 10-H); 9.23 and 7.86 (AB spectrum protons 2- and 3-H, J = 4.6 Hz); 7.8 (5H, m, 5- to 9-H); paracyclophane ring: 6.7 (7H, m, H_{arom}); 2.9 ppm (8H, m, H_{aliph}). ^{13}C NMR spectrum: 148.5; 146.5; 140.4-139.4; 136.0; 131.5 and 124.8 (10 × C_{quat}); 148.5; 136.0-122.5 and 116.4 (15 × CH); 35.5-34.3 ppm (4 × CH_2).

This work was carried out with the support of GKRF at VO NTP "Fine Organic Synthesis" (grant FT-15).

REFERENCES

1. L. I. Kryvenko, B. N. Anisimov, T. P. Khrustoforova, S. A. Soldatova, and A. T. Soldatenkov, Khim. Geterotsikl. Soedin., No. 8, 1055 (1997).
2. A. T. Soldatenkov, I. A. Bektro, Zh. A. Mamyrbekova, S. A. Soldatova, and A. I. Chernyshev, Khim. Geterotsikl. Soedin., No. 5, 653 (1997).
3. N. K. Kochetkova (ed.), General Organic Chemistry [in Russian], Khimiya, Vol. 8, Moscow (1985), p. 91.
4. L. S. Novikov, V. A. Mezhentsev, and I. G. Tishchenko, Khim. Geterotsikl. Soedin., No. 12, 1693 (1979).
5. V. G. Kharchenko, L. I. Markova, T. K. Kazarinova, and L. M. Yubovich, Khim. Geterotsikl. Soedin., No. 6, 846 (1985).
6. S. I. Zav'yalov, A. G. Zavvozin, O. V. Dorofeeva, and E. E. Rumyantseva, Izv. Akad. Nauk SSSR., Ser. Khim., No. 2, 509 (1991).