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NOVEL FUSED TRIHETEROCYCLIC SYSTEMS.
SYNTHESIS OF 6H-PYRIDO[2,3-c]PYRROLO[1,2-e]-1,2,5-TRIAZEPINES

Jean-Charles Lancelot, Daniel Ladurée, Hussein El Kashef*, and Max Robba**
Laboratoire de Chimie Thérapeutique, U.E.R. des Sciences Pharmaceutiques.
Université de Caen, 1, rue Vaubénard, 14032 Caen-Cédex,
FRANCE

Abstract — The synthesis of 6H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepines has been described.

This communication presents a facile synthetic approach to the unknown pyridine isoster of benzopyrrolotriazepine[1]. This, 3-amino-2-chloropyridine (1a) was interacted with 2,5-dimethoxytetrahydrofuran in boiling acetic acid following the procedure of Clauson-Kaas[2] to give 2-chloro-3-(N-pyrryl)-pyridine (2a). The 2-chlorine atom of the latter compound was easily replaced by a hydrazino group giving the derivative (3). Heating this hydrazino derivative in acetic anhydride resulted in acetylation with concomitant cyclodehydration leading to 3-methyl-8-(N-pyrryl)-1,2,4-triazolo[4,3-a]pyridine (4).

Another cyclization involving the pyridine nitrogen could be realised by heating (3) with acetylacetone to give 3,5-dimethyl-10-(N-pyrryl)-pyrido[2,1-c]-1,2,4-triazepine (5), bp 180°C at 0.05mm, nmr ; 8.46 (1H, dd, H7, JH7-H9=1.50 Hz, JH7-H8=4.50 Hz) ; 8.08 (1H, dd, H9, JH9-H8=7.80 Hz, JH9-H7=1.50 Hz) ; 7.60 (1H, dd, H8, JH8-H7=4.50 Hz, JH8-H9=7.80 Hz) ; 5.91 (1H, s, H4) ; 6.51 (2H, t, H2', H5') ; 6.08 (2H, t, H3', H4') ; 2.18 (3H, s, CH_3) ; 1.78 (3H, s, CH_3).

The reactivity of the α-position in pyrrole towards electrophiles made it possible to apply both Vilsmeier-Haack and Friedel-Crafts reactions on compound (2a) to give the formyl and acyl derivatives (6a-c). The formyl derivative (6a) was converted into its oxime which was immediately[3] treated with acetic anhydride yielding the corresponding cyano compound (6d). When compounds (6a-d) were heated under reflux with hydrazine hydrate, the title compounds (7a-d) were obtained. Acetylation of (7d) resulted in the diacetyl derivative (8). On the other hand, the 6H-8-hydrazinopyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepine (7e) could be obtained when 3-amino-2,5-dichloropyridine (1b) was used instead of (1a) as starting material. Further synthetic studies are in progress.

Physical and analytical data :

Compounds (1a-1b) are commercially available (ALDRICH). All elemental analyses are in accordance with the structures proposed. Nmr spectra were measured on VARIAN-EM390 90 MHz using DMSO-d_6 as a solvent and TMS as internal reference.

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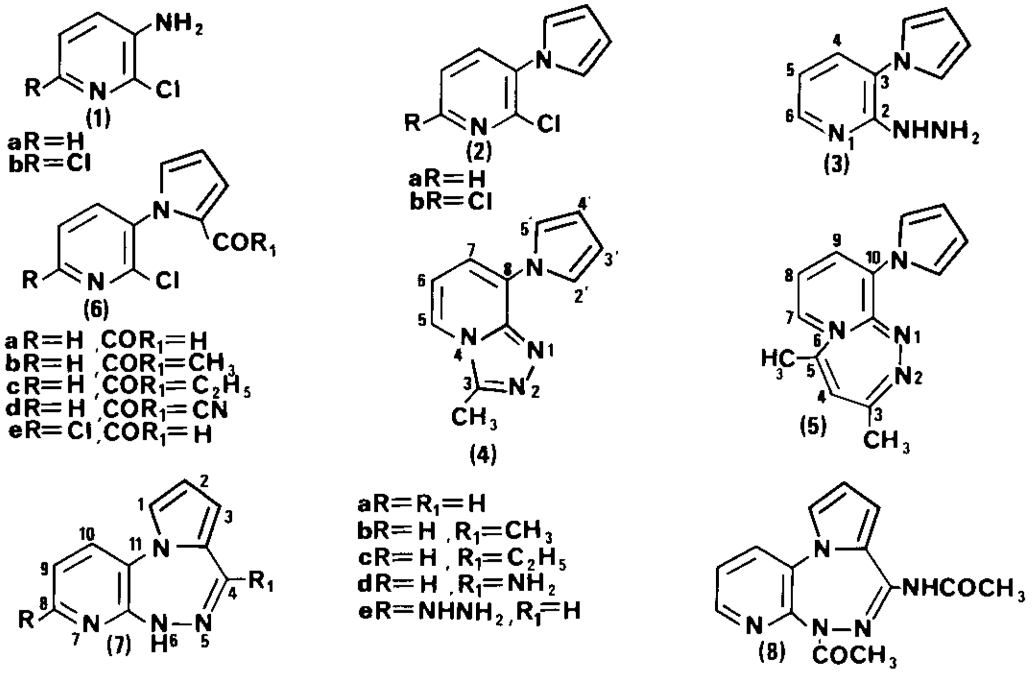
* Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt.

** To receive any correspondence.

TABLE



(2a), bp 154°C at 0.05mm, nmr ; 8.38 (1H, dd, H6, JH6-H4=1.80 Hz, JH6-H5=4.5 Hz) ; 7.88 (1H, dd, H4, JH4-H5=7.8 Hz) ; 7.30 (1H, dd, H5, JH5-H4=7.8 Hz) ; 7.30 (2H, t, H2'-H5') ; 6.25 (2H, t, H3'-H4') ; (2b), bp 140°C at 0.05mm, nmr ; 7.35 (1H, d, H4, JH4-H5=8.1 Hz) ; 7.60 (1H, d, H5, JH5-H4=8.1 Hz) ; 7.00 (2H, t, H2'-H5') ; 6.25 (2H, t, H3'-H4') ; (3), mp 74°C, nmr ; 8.11 (1H, dd, H6, JH6-H4=1.62 Hz, JH6-H5=4.8 Hz) ; 7.38 (1H, dd, H4, JH4-H5=7.50 Hz) ; 6.71 (1H, dd, H5, JH5-H4=7.50 Hz) ; 6.91 (2H, t, H2'-H5') ; 6.26 (2H, t, H3'-H4') ; 6.45 (1H, s, NH) ; 4.2 (2H, s, NH$_2$) ; (4), mp 186°C, nmr ; 8.20 (1H, dd, H5, JH5-H6=6.60 Hz, JH5-H7=0.72 Hz) ; 7.95 (1H, dd, H7, JH7-H6=7.20 Hz) ; 7.00 (1H, dd, H6, JH6-H5=6.60 Hz, JH6-H7=7.20 Hz) ; 7.95 (2H, t, H2'-H5') ; 6.31 (2H, t, H3'-H4') ; (6a), mp 146°C, nmr ; 9.46 (1H, d, CHO, JH5'-CHO=0.9 Hz) ; 8.48 (1H, dd, H6, JH6-H4=1.8 Hz, JH6-H5=4.5 Hz) ; 7.95 (1H, dd, H4, JH4-H6=1.8 Hz, JH4-H5=7.8 Hz) ; 7.55 (1H, dd, H5, JH5-H6=4.5 Hz) ; 7.36 (1H, dd, H5', JH5'-H3'=1.8 Hz, JH5'-H4'=2.7 Hz) ; 7.23 (1H, dd, H3', JH3'-H5'=1.8 Hz, JH3'-H4'=3.9 Hz) ; 6.50 (1H, dd, H4', JH4'-H3'=3.9 Hz, JH4'-H5'=2.7 Hz) ; (6b), mp 106°C, nmr ; 8.46 (1H, dd, H6, JH6-H4=1.8 Hz, JH6-H5=4.5 Hz) ; 7.81 (1H, dd, H4, dd, H4, JH4-H6=1.8 Hz, JH4-H5=7.8 Hz) ; 7.45 (1H, dd, H5, JH5-H6=4.5 Hz, JH5-H4=7.8 Hz) ; 7.21 (1H, dd, H5', JH5'-H3'=1.8 Hz, JH5'-H4'=2.7 Hz) ; 7.16 (1H, dd, H3', JH3'-H4'=3.9 Hz, JH3'-H5'=1.8 Hz) ; 6.35 (1H, dd, H4', JH4'-H3'=3.9 Hz, JH4'-H5'=2.7 Hz) ; 2.31 (1H, s, CH$_3$) ; (6c), mp 72°C, nmr ; 8.46 (1H, dd, H6, JH6-H4=1.8 Hz, JH6-H5=4.5 Hz) ; 8.00 (1H, dd, H4, JH4-H6=1.8 Hz, JH4-H5=7.8 Hz) ; 7.55 (1H, dd, H5, JH5-H4=7.8 Hz, JH5-H6=4.5 Hz) ; 7.86 (1H, dd, H5', JH5'-H3'=2.1 Hz, JH5'-H4'=1.8 Hz) ; 7.08 (1H, dd, H3', JH3'-H4'=3 Hz, JH3'-H5'=2.1 Hz) ; 6.61 (1H, dd, H4', JH4'-H3'=3 Hz, JH4'-H5'=1.8 Hz) ; 2.76 (2H, dd, CH$_2$) ; 1.05 (3H, t, CH$_3$) ; (6d), mp 98°C, nmr ; 8.56 (1H, dd, H6, JH6-H4=1.62 Hz, JH6-H5=4.8 Hz) ; 8.15 (1H, dd, H4, JH4-H6=1.62 Hz, JH4-H5=7.50 Hz) ; 7.63 (1H, dd, H5, JH5-H6=4.8 Hz, JH5-H4=7.50 Hz) ;

7.41 (1H, dd, H5', JH5'-H3'=1.5 Hz, JH5'-H4'=2.7 Hz) ; 7.20 (1H, dd, H3', JH3'-H5'=1.5 Hz, JH3'-H4'=3.9 Hz) ; 6.41 (1H, dd, H4', JH4'-H5'=2.7 Hz, JH4'-H3'=3.9 Hz) ; (6e), mp 148°C, nmr ; 8.03 (1H, d, H4, JH4-H5=8.10 Hz) ; 7.66 (1H, d, H5, JH5-H4=8.10 Hz) ; 7.35 (1H, dd, H5', JH5'-H3'=1.8 Hz, JH5'-H4'=2.7 Hz) ; 7.21 ((1H, dd, H3', JH3'-H4'=3.9 Hz, JH3'-H5'= 1.8 Hz) ; 6.45 (1H, dd, H4', JH4'-H5'=2.7 Hz, JH4'-H3'=3.9 Hz) ; 9.45 (1H, s, CHO) ; (7a), mp 176°C, nmr ; 9.00 (1H, dd, H4, JH4-H1=0.6 Hz) ; 8.70 (2H, m, H8, H10) ; 8.51 (1H, m, H1) ; 8.05 (1H, s, NH) ; 7.55 (1H, dd, H9, JH9-H8=4.8 Hz, JH9-H10=7.80 Hz) ; 6.96 (2H, m, H2, H3) ; (7b), mp 142°C, nmr ; 8.50 (1H, s, NH) ; 7.95 (1H, dd, H8, JH8-H10=1.5 Hz, JH8-H9=4.8 Hz) ; 7.66 (1H, tt, H10-H8=1.5 Hz, JH10-H9=7.80 Hz, JH10-NH=0.84 Hz) ; 7.26 (1H, dd, H1, JH1-H2= 2.7 Hz, JH1-H3=1.56 Hz) ; 6.95 (1H, dd, H9, JH9-H10=7.80 Hz, JH9-H8=4.8 Hz) ; 6.55 (1H, dd, H3, JH3-H1=1.56 Hz, JH3-H2=3.90 Hz) ; 6.28 (1H, dd, H2, JH2-H1=2.70, JH2-H3=3.90 Hz) ; 2.15 (3H, s, CH_3) ; (7c), mp 120°C, nmr ; 9.33 (1H, s, NH) ; 8.01 (1H, dd, H8, JH8-H10=1.5 Hz, JH8-H9=4.8 Hz) ; 7.71 (1H, tt, H10, JH10-H9=7.80 Hz, JH10-H8=1.5 Hz) ; 7.30 (1H, dd, H1, JH1-H2=2.7 Hz, JH1-H3=1.56 Hz) ; 7.00 (1H, dd, H9, JH9-H8=4.8 Hz, JH9-H10=7.80 Hz) ; 6.58 (1H, dd, H3, JH3-H2=3.90 Hz, JH3-H1=1.56 Hz) ; 5.98 (1H, dd, H2, JH2-H3=3.90 Hz, JH2-H1= 2.7 Hz) ; 2.70 (2H, dd, CH_2) ; 1.10 (3H, t, CH_3) ; (7d), mp 214°C, nmr ; 8.00 (2H, m, H8, H10) ; 7.86 (1H, dd, H1, JH1-H2=2.7 Hz, JH1-H3=1.56 Hz) ; 7.25 (1H, dd, H3, JH3-H1=1.56 Hz, JH3-H2=3.90 Hz) ; 6.78 (1H, dd, H9, JH9-H8=4.8 Hz, JH9-H10=7.80 Hz) ; 6.53 (1H, dd, H2, JH2-H1=2.7 Hz, JH2-H3=3.90 Hz) ; 5.61 (2H, s, NH_2) ; 5.40 (1H, s, NH) ; (7e), mp 238°C, nmr ; 9.03 (1H, s, H4) ; 8.81 (1H, d, H10, JH10-H9=8.4 Hz) ; 8.55 (1H, dd, H1, JH1-H2=2.70 Hz, JH1-H3=1.56 Hz) ; 7.65 (1H, d, H9, JH9-H10=8.4 Hz) ; 7.40 (2H, s, NH_2) ; 7.05 (1H, dd, H3, JH3-H2=1.56 Hz, JH3-H1=1.56 Hz) ; 6.95 (1H, dd, H2, JH2-H3=3.90 Hz, JH2-H1=2.7 Hz) ; 3.45 (1H, s, NH) ; (8), mp 262°C, nmr ; 8.38 (1H, dd, H8, JH8-H10=1.50 Hz, JH8-H9=4.8 Hz) ; 8.13 (3H, m, H1, H10, NH) ; 7.20 (1H, dd, H9, JH9-H8=4.8 Hz, JH9-H10=7.80 Hz) ; 6.85 (1H, dd, H3, JH3-H1=1.56 Hz, JH3-H2=3.90Hz) ; 6.60 (1H, dd, H2, JH2-H3=3.90 Hz, JH2-H1=2.7 Hz) ; 2.30 (3H, s, $COCH_3$) ; 2.08 (3H, s, $COCH_3$).

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2) N. Clauson-Kaas and Z. Tyle, Acta Chem. Scand., 6, 667, (1952) ; N. Elming and N. Clauson-Kaas, Ibid., 6, 867, (1952).

3) This oxime was not isolated because it decomposes with a violent explosion on standing.

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