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SYNTHESIS OF A NEW BRIDGED DIAMINE 3,6-DIAZABICYCLO [3.2.0] HEPTANE: APPLICATIONS TO THE SYNTHESIS OF QUINOLONE ANTIBACTERIALS.

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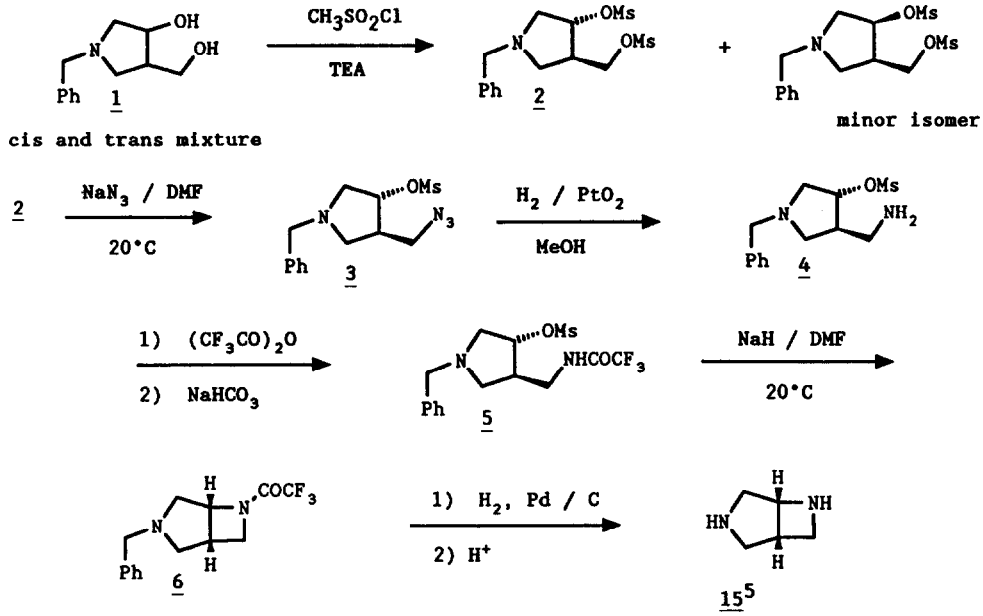
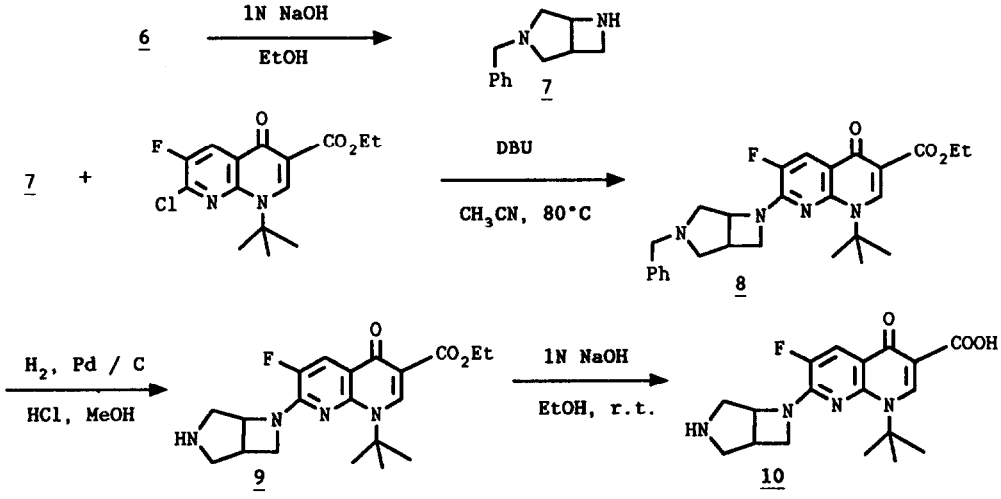
Abstract: Diprotected 3,6-diazabicyclo [3.2.0] heptane has been prepared by an highly efficient process. Selective deprotection, followed by condensation with 7-halogenoquinolones led to the naphthyridones 10 and 13 and the quinolone 14.

Our general interest[1] in azetidines, pyrrolidines and piperazines led us to examine new bridged diamines including pyrrolidine and azetidine moieties. We report here a convenient preparation of the 3,6-diazabicyclo [3.2.0] heptane.

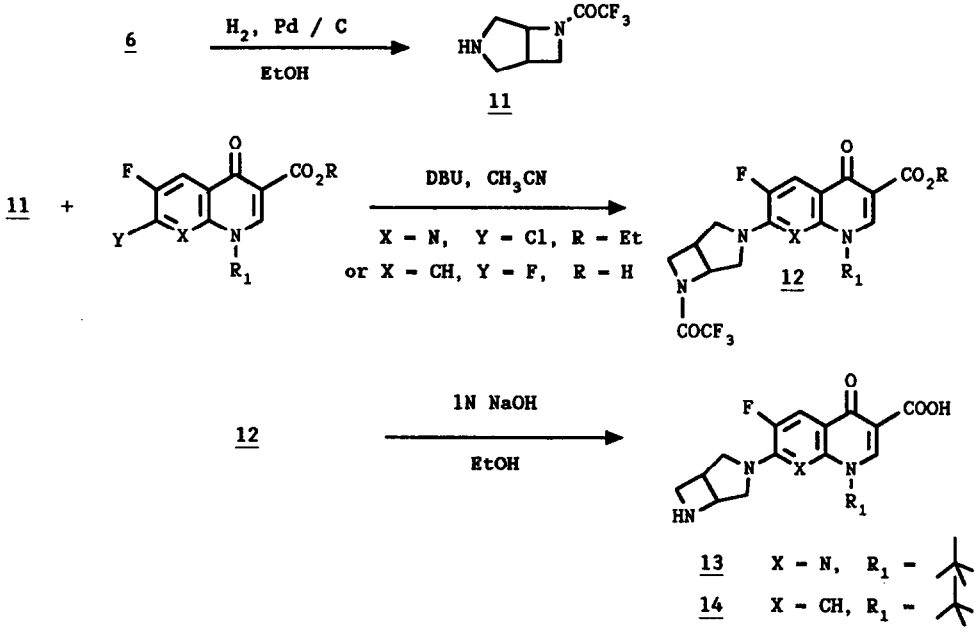
Pyrrolidine 1 (cis and trans mixture)[2] was reacted with methanesulfonyl chloride in the presence of TEA to afford trans dimesylate[3] 2 (78%) purified by HPLC (silica gel, 4:1 CH_2Cl_2-EtOAc). Treatment of 2 with an equimolecular amount of sodium azide in DMF at room temperature gave the monoazide 3. Reduction of 3 over PtO_2 under a hydrogen atmosphere followed by treatment with trifluoroacetic anhydride gave 5 (60% from 3). Cyclisation of 5 in DMF in presence of NaH at room temperature furnished the diprotected cis-diamine 6[4] in 97% yield.



Deprotection of the azetidinyl part of **6** with ethanolic 1N NaOH at 80°C gave **7** which could be condensed with ethyl 7-chloro-1,8-naphthyridone-3-carboxylate to give **8**, which was hydrogenated over Pd on C in presence of hydrochloric acid in methanol. Alkaline hydrolysis of **9** with 1N NaOH at room temperature afforded naphthyridone **10**.



Deprotection of the pyrrolidinyl part of **6** was performed by catalytic hydrogenolysis (H_2, Pd/C) in ethanol to give **11** which was condensed with 7-chloro-1,8-naphthyridone or quinolone-3 carboxylic acids to afford **12**. Basic hydrolysis of **12** in ethanol gave the corresponding naphthyridone and quinolone-3-carboxylic acids **13** and **14**.



Some of these novel compounds displayed a substantial antibacterial activity: structure-activity relationships and biological data will be reported elsewhere.

Acknowledgement: We thank Dr. J. Saint-Germain for spectral determinations and M. Massoudi for technical assistance.

References and notes

1)a) Bouzard,D.; Di Cesare,P.; Essiz, M.; Jacquet,J.P.; Remuzon,P.; Weber,A.; Oki,T.; Masuyoshi,M.; J. Med. Chem., **1989**, 32, 357.

b) Bouzard,D.; Di Cesare,P.; Essiz, M.; Jacquet,J.P.; Kiechel,J.R.; Remuzon,P.; Weber,A.; Oki,T.; Masuyoshi,M.; Kessler,R.E.; Fung-Tomc,J.; Desiderio,J.; J. Med. Chem., **1990**, 33, 1344.

c) Remuzon,P.; Bouzard,D.; Di Cesare,P.; Essiz,M.; Jacquet,J.P.; Kiechel,J.R.; Ledoussal,B.; Kessler,R.E.; J. Fung-Tomc, J. Med. Chem., **1991**, 34, 29.

2) Jaeger,E.; Biel,J.H.; J. Org. Chem., **1965**, 30, 740.

3) Trans and cis dimesylate were determined by NOE experiment on a 200MHz Bruker NMR apparatus.

4)a) This product **6** (oil) has been identified by highly-resolution 1H-NMR: (200MHz, $CDCl_3$); 2.50-2.90 (CH_2N, H_1, 4H, 2m); 3.04 (CHN, 1H, dd); 3.56(CH_2N, 2H, q);3.68(CH_2-Ph, 2H, s);4.75(H_4, 1H, m);7.29(5H, Ar, m) and MS (70eV) 284 M^+.

b) After completion of our work , the related diamine 3-benzyl-6-*tert*-butoxycarbonyl 3,6-diazabicyclo [3.2.0] heptane, synthetised via an other process appeared in a Japanese patent/JP 8956, 673; Chem. Abstr. **1989**, 111, 153779W.

c) Attempts to exchange the mesyl group of **5** with tetrabutyl ammonium fluoride in THF to give the corresponding fluoro- pyrrolidine failed. It was obtained exclusively the diamine **6**.

5) Diamine **15** as dimaleate, white needles, m.p. 180°C, was characterized by 1H NMR, (200MHz, DMSO d6); 2.38(H_1, 1H, m);2.87-3.43(CH_2N, 6H,m); and by elemental analysis.

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