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NEW HETEROCYCLES - ACCESS TO THIENO[3,2,b][f] AND THIENO[2,3,b][f]BENZAZEPINE DERIVATIVES

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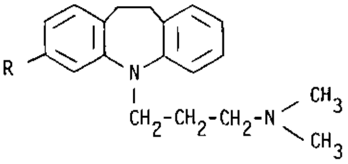
Abstract - The synthesis of the new heterocycles in the title is described. From these, the thieno analogues of imipramine and clomipramine were prepared.

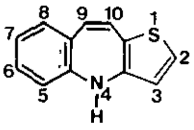
Imipramine I and clomipramine II are among the most active dibenzazepine derivatives commonly used in the treatment of depressive illnesses. However, this type of compound is not devoid of undesirable side-effects and, nowadays, a lot of work is still done with the view of finding new and better tolerated representatives.

I R = H
II R = Cl



In our own contribution to this therapeutic field we have prepared the corresponding bioisosteres of I and II where one of the two benzenoid rings is replaced by a thiophene ring. In many other series this type of modification has often retained the main biological profile of the parent drugs.

Of the three possible thienobenzazepine isomeres III, IV and V not previously synthesized, we chose to study the access to the thieno[3,2,b][f]benzazepine III and the thieno[2,3,b][f]benzazepine IV together with the corresponding 9,10 and 4,5- dihydro derivatives from which the thieno analogues of imipramine were prepared. This communication is mainly relative to the synthesis of these two new molecular skeletons.



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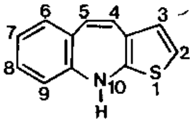

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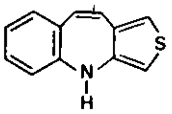
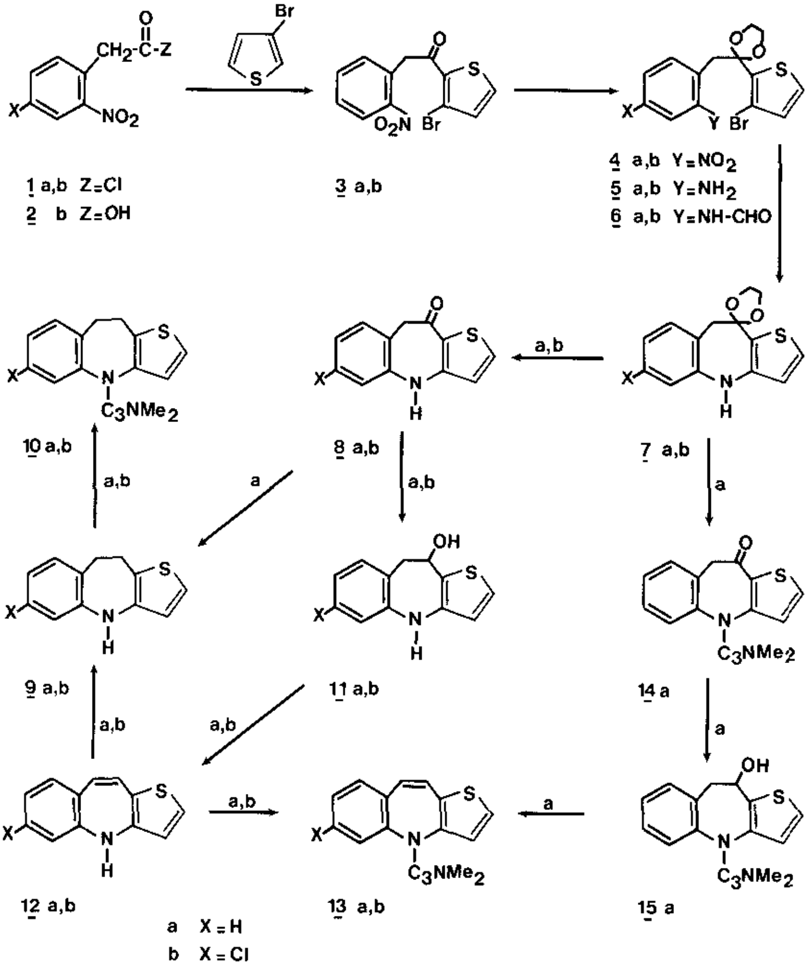


.V.

1) Thieno[3,2,b][f]benzazepines and their 9,10-dihydro derivatives.

By analogy with the synthesis of 10,11-dihydro[5H]dibenz[b,f]azepines (1) the 9,10-dihydrothieno [3,2,b][f]benzazepine derivatives were synthesized by the intramolecular cyclization of the key intermediate 5a which was prepared by the following short sequence of reactions (Scheme A).



SCHEME A

The condensation of 2-nitrophenyl acetyl chloride 1a (0.55 mole) (2) with 3-bromothiophene (0.55 mole) in benzene at room temperature using $SnCl_4$ (0.55 mole) as a catalyst led to a mixture of two isomeric ketones in which the desired product 3a was predominant. Prior to the reduction of the nitro group the ketone function was transformed into the corresponding ketal by heating the mixture of ketones in ethylene glycol at 150°C in the presence of p-toluenesulfonic acid (0.055 mole). By crystallization of the crude product mixture the ketal derivative 4a, $C_{14}H_{12}NO_4S$, mp 112°, was obtained in 51% yield. The position of the side chain on the thiophene ring was determined by NMR spectral analysis ($CDCl_3$) in which the C_4-C_5 proton resonances were observed as doublets (J = 5Hz) at 6.96 and 7.16 ppm respectively. Subsequent reduction of 4a with Zn in acetic acid led in excellent yield (98%) to the desired amino derivative 5a, $C_{14}H_{14}BrNO_2S$, mp 71°; νmax ($CHCl_3$) 3428 and 3344 cm^{-1}. Cyclisation of 5a (1 mole) could be accomplished directly as described in the phenothiazine series (3) by treatment in refluxing DMF with K_2CO_3 (1.2 mole) in the presence of Cu powder (0.5 mole) and a small amount of iodine (0.08 mole). However, more reproducible results were obtained with the corresponding N-formyl derivative 6a prepared from 5a by action of H-COOH with DCC in ethyl acetate as already described in ref. (4). In this case, the cyclisation occurs with good yield after 22h reflux in mesitylene with K_2CO_3 and Cu powder. Alkaline hydrolysis of the crude product gave 7a, $C_{14}H_{13}NO_2S$, mp 165°, in 82% yield from 5a; νmax ($CHCl_3$) 3440 cm^{-1}; λmax (EtOH) 232, 257 and 301 nm (ε = 12500, 7400 and 10000). The ketone intermediate 8a was subsequently obtained in 95% yield by acid hydrolysis (conc. HCl-EtOH) of the ketal, $C_{12}H_9NOS$, mp 195°; νmax ($CHCl_3$) 3402, 1643 and 1636 cm^{-1}; λmax (EtOH) 245, 275 and 360 nm (ε = 18750, 7100 and 9000).

The carbonyl group of 8a was completely reduced with $LiAlH_4$-$AlCl_3$ (3.5/1 mole) in THF at 20° to give the 9,10-dihydro-4H-thieno[3,2,b][f]benzazepine 9a, $C_{12}H_{11}NS$, mp 114°, in 100% yield; νmax ($CHCl_3$) 3416 cm^{-1}; λmax (EtOH) 229, 265 and 304 nm (ε = 12800, 8060 and 8200); ^{1}H-NMR ($CDCl_3$) 3.07 (4H,s, the CH_2 of the central ring) or partially reduced by $NaBH_4$ in dioxane-water 9/1 at 50° to give the alcohol 11a. Acidic treatment of 11a under different conditions led only to complex mixtures of products, but it was found that the hydroxyl group could be cleanly eliminated under neutral conditions by refluxing in benzene with Al_2O_3 CBT 1 (PECHINEY). The 4H-thieno[3,2,b][f] benzazepine 12a, $C_{12}H_9NS$, mp 187°, was thus obtained in 90% yield from 8a; νmax ($CHCl_3$) 3401 cm^{-1}; λmax (EtOH) 238 and 270 nm (ε = 13600 and 22000); ^{1}H-NMR ($CDCl_3$) 6 (2H,s, ethylenic H).

N-Alkylation of 9a and 12a by reaction with 3-chloropropyldimethylamine and NaH in refluxing xylene (9a) or THF-HMPT 2/3 (12a) produced the desired derivatives 10a (100% yield), $C_{17}H_{22}N_2S$; λmax (EtOH) 268 and 295 nm (ε = 5800 and 4550); ^{1}H-NMR ($CDCl_3$) 1.79 (2H,q, -CH_2-) 2.13 (6H,s, NMe_2) 2.3 (2H,t, -CH_2-NMe_2) 3.08 (4H,s, the CH_2 of the central ring) 3.76 (2H,t, N-CH_2-), and 13a, obtained as its fumarate (64% yield), mp 170 - 172°; λmax (EtOH) 211, 263 and 363 nm (ε = 30150, 18800 and 1500); ^{1}H-NMR ($CDCl_3$) of the basis : 1.8 (2H,m, -CH_2-) 2.19 (6H,s, NMe_2) 2.46 (2H,t, -CH_2-NMe_2) 3.55 (2H,t, $>$N-CH_2-) 6.55 (2H,s, ethylenic H).

An alternative and more efficient route to 13a which does not necessitate purification of intermediate products involved alkylation of the ketal 7a with 3-chloropropyldimethylamine as above, followed by acidic hydrolysis (N Aq HCl) of the ketal group. The crude ketone derivative 14a was reduced by sodium diethylaluminium hydride in toluene for 2h at 20° and the resulting alcohol 15a was directly converted into the fumaric salt of the thienobenzazepine 13a by heating in ethanol with fumaric acid, (5).

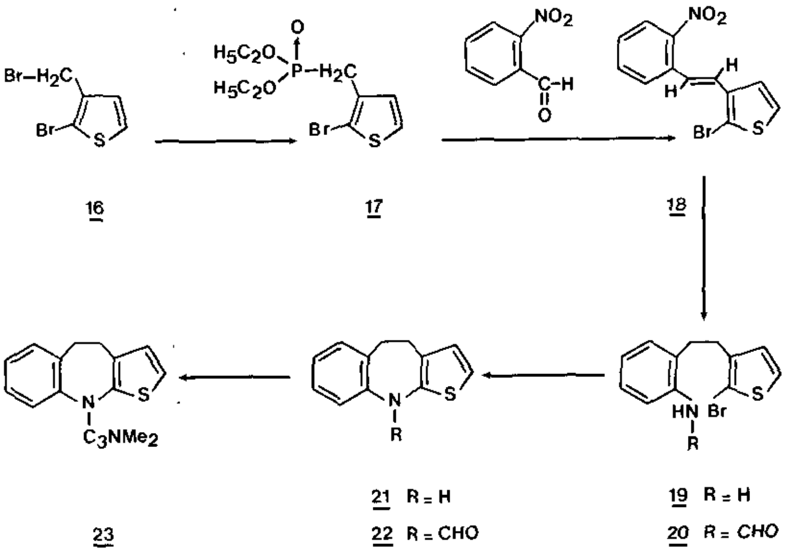
The corresponding chloro derivatives 10b and 13b were prepared by a similar alkylation of the chloro intermediates 9b and 12b. The chlorothienobenzazepine 12b was obtained via 8b and 11b according to the method already described for 12a, starting from 4-chloro-2-nitrophenylacetic acid 2 (6). In this series the dihydro compound 9b was prepared by catalytic hydrogenation of 12b with Pd/charcoal in ethanol. The yields and the physical constants of the intermediary derivatives are given in Table I.

Products	Formula	mp	Yield %
3b	$C_{12}H_7BrClNO_3S$	146 - 147°	35
4b	$C_{14}H_{11}BrClNO_4S$	79°	95
5b	$C_{14}H_{13}BrClNO_2S$	88°	71
6b	$C_{15}H_{13}BrClNO_3S$	110°	90
7b	$C_{14}H_{12}ClNO_2S$	141°	70
8b	$C_{12}H_8ClNOS$	285°	96
9b	$C_{12}H_{10}ClNS$	112°	80
10b	$C_{17}H_{21}ClN_2S$ (oxalic acid)	180°	88
12b	$C_{12}H_8ClNS$	200°	100
13b	$C_{17}H_{19}ClN_2S$ (oxalic acid)	128 et 150°	73

TABLE I

2) 4,5-dihydro-10H-thieno[2,3,b][f]benzazepine 21 (Scheme B)

To obtain the tricyclic intermediate 21 we needed a 2-bromothienyl derivative such as 19 with a 2-aminophenylethyl substituant in position 3. As the Friedel-Crafts condensations on 2-bromothiophene provide only 5-substituted products (7) we used a different route, starting from 2-bromo-3-bromomethylthiophene 16 (8) as represented in Scheme B.



SCHEME B

Treatment of 16 with triethyl phosphite at 160° for 4h gave rise to the diethyl phosphonate 17, $C_9H_{14}BrO_3PS$, $bp_{0.1\ mm}$ = 110° (87% yield) which was then treated with NaH in dimethoxyethane (9) and condensed with 2-nitrobenzaldehyde at room temperature. Usual work up afforded the ethylenic derivative 18 in 75% yield which was shown from its NMR spectrum to be the trans isomer only, $C_{12}H_8BrNO_2S$, mp 94°; νmax ($CHCl_3$) 1630 cm^{-1}; λmax (EtOH) 213 and 281 nm (ε = 17300 and 17600); ^1H-NMR ($CDCl_3$) 7.02 (1H,d, J = 15.5 Hz, ethylenic H). Before cyclisation, both the NO_2 and C=C of 18 were reduced in one step by treatment with hydrazine in the presence of air in refluxing diethylene glycol according to (10). Compound 19, obtained as a yellow oil, was purified by conversion to its hydrochloride and subsequent liberation of the free base (55% yield); λmax (EtOH) 236 and 286 nm (ε = 15300 and 2450).

By analogy with the formation of 7a, cyclisation of 19 was accomplished using its N-formyl derivative 20 prepared from 19 by action of formyl acetic anhydride in benzene at room temperature (77% yield), $C_{13}H_{12}BrNOS$, mp 155°; νmax ($CHCl_3$) 1693 cm^{-1}. Compound 22 was obtained in 78% yield when the reaction was carried out in refluxing mesitylene, $C_{13}H_{11}NOS$, mp 118°; νmax ($CHCl_3$) 1689, 1683 cm^{-1}; λmax (EtOH) 248 nm (ε = 7200); ^1H-NMR ($CDCl_3$) 3.03 (4H,s, CH_2 of the central ring) 6.62 (H_1, d, J = 5.5Hz) 7.04 (H_2,d, J = 5.5Hz) 8.47 (2/3) and 8.80 (1/3) (1H, rotamers, $H\text{-}\overset{O}{\overset{\|}{C}}\text{-}$). The free amine 21 was found to be unstable as observed for 2-aminothiophene (11) and could not be isolated. However, N-alkylation of 21 with 3-chloropropyldimethylamine could be carried out in refluxing

THF-HPMT for 5h on the sodium salt derivative prepared from *22* beforehand *in situ* with sodium methoxide in refluxing THF. After purification by column chromatography (silicagel H $CHCl_3$-MeOH 75/25) the desired N-dimethylaminopropyl derivative *23* was obtained as an oil, in 61% yield. Its hydrochloride was crystallized, $C_{17}H_{22}N_2S$, HCl, mp 170° and characterized; λmax (EtOH) 280 nm (ε = 7350); ^{1}H-NMR ($CDCl_3$) 2.8 - 3.2 (6H,m, the CH_2 of the central ring, CH_2-NMe_2) 2.67 (6H,s, CH_3) 3.83 (2H,t, J = 6Hz, other N-CH_2).

Among the compounds synthesized and examined on the pharmacological tests for antidepressant activity, the unsaturated derivative *13a* (RU 15687), belonging to the first series, appeared to be the most interesting. In animal experiments, its pharmacological profile is similar to that of imipramine but with a lesser degree of acute cardiac toxicity.

References

1. See L.J. Kricka and A. Ledwith, *Chem. Rev.* 1974, **74**, 101.
2. P.W. Neber, K. Hartung and W. Ruopp, *Chem. Ber.* 1925, **58**, 1234.
3. H.M. Grotta, T.F. Page Jr., C.J. Riggle and A.A. Manian, *J. Het. Chem.* 1967, **4**, 611.
4. H.L. Yale, B. Beer, J. Pluscec and E.R. Spitzmiller, *J. Med. Chem.* 1970, **13**, 713.
5. J. Jolly and J. Warnant, Personal communication.
6. W.B. Wright Jr., and K.H. Collins, *J. Am. Chem. Soc.* 1956, **78**, 221. J.R. Piper and F.J. Stevens, *J. Het. Chem.* 1966, **3**, 95.
7. G.A. Olah, "Friedel-Crafts and related reactions", Vol. III, Ed. by Interscience Publishers, J. Wiley & Sons Inc., New York - London - Sydney, 1964, p. 88.
8. E. Campaigne and W.M. Lesuer, *J. Am. Chem. Soc.* 1949, **71**, 333.
9. W.S. Wadsworth Jr., and W.D. Emmons, *J. Am. Chem. Soc.* 1961, **83**, 1733.
10. Huang-Minlon, *J. Am. Chem. Soc.* 1948, **70**, 2802.
11. D.L. Eck and G.W. Stacy, *J. Het. Chem.* 1969, **6**, 147.

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