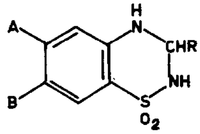
Tetrahedron Letters No.33, pp. 3949-3952, 1966. Pergamon Press Ltd.
Printed in Great Britain.

EFFECT OF SOME REDUCTION AGENTS ON 3-SUBSTITUTED DIHYDROBENZOTHIADIAZINES AND 4-QUINAZOLONES - CLEAVAGE OF THE HETEROCYCLIC RING.

M.G.Biressi, M.Carissimi and F.Ravenna
MAGGIONI e C. - S.p.A. - MILANO (Italy) - Research Laboratories

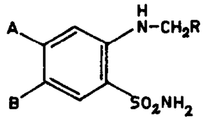
(Received 15 June 1966)

During our studies on some new derivatives of dihydrochlorothiazide (Ia; R = H) we submitted to the action of reducing agents this compound as well as several of its derivatives (Ia; R = alkyl, aralkyl or aryl) bearing in mind that, in spite of preceeding work (1), it was not yet fully clear if the above compounds possessed an azomethine or a dihydrobenzothiadiazine structure.



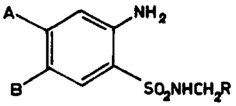
Ia A=Cl B=SO_2NH_2

Ib A=B=H



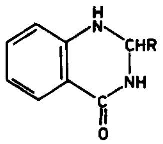
IIa A=Cl B=SO_2NH_2

IIb A=B=H

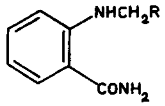


IIIa A=Cl B=SO_2NH_2

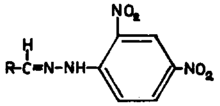
IIIb A=B=H



IV



V



VI

While by catalytic hydrogenation with various catalysts (PtO_2; Pd on C, Pd on $BaSO_4$) or by reaction with $LiAlH_4$ we isolated only the unchanged starting material, if we treated Ia where R was aryl with trimethylamineborane (TMAB) in acetic acid and with $NaBH_4$ in methanol, we isolated, according to the reducing agent used, two different substances having identical elementary composition but the structures respectively IIa and IIIa. IIa and IIIa where R was phenyl had been already synthesized by an unambiguous route (2).

We did not succeed in isolating both IIa and IIIa from every Ia we allowed to react with the reducing reagents: this happened only when R was phenyl, 4-chlorophenyl and 3,4,5-trimethoxyphenyl. From Ia where R was n.hexyl and 4-nitrophenyl we isolated IIa with TMAB and unchanged starting material with $NaBH_4$, while on the contrary from Ia where R was 4-diphenylyl and 4-sulfonamidophenyl IIIa were isolated with $NaBH_4$ and starting material with TMAB. When R was ethyl and benzyl the starting material was recovered with both the reducing agents. All compounds isolated by the reaction with $NaBH_4$ possessed an aromatic amino group which could be diazotized and coupled and two I.R. absorption bands between 3450 - 3505 and 1640 - 1620 cm^{-1}, which did not exist in IIa and Ia.

The reductive cleavage of the ring was further investigated on the unsubstituted dihydrobenzothiadiazines Ib, where it proceeded mo=

re regularly and with by far better yields (*).

Compounds where R was benzyl, phenyl, 2-, 3-, and 4-chlorophenyl, 4-nitrophenyl, 4-biphenylyl and 4-sulfonamidophenyl gave by reacting with TMAB the IIb derivatives and with $NaBH_4$ the IIIb ones. From the two derivatives where R was alkyl (ethyl and n.hexyl) we isolated IIa by reaction with TMAB and starting material with $NaBH_4$.

We also investigated in this respect the behaviour of some dihydro-4-quinazolones IV (4). When R was phenyl, 4-chlorophenyl and 4-sulfonamidophenyl the anthranilamide derivatives V were isolated with TMAB, and the starting material with $NaBH_4$;when R was ethyl the starting material was recovered with both reagents.

In the attempt to explain the different reactivities observed we tried to evaluate the stability of the dihydrobenzothiadiazine ring of compounds Ia by determinating the 2,4-disulfonamido-5-chloroaniline. formed by keeping them 16 hr. at +5° in methanol containing 20% of dil. HCl (5). We found that the substances which did not react either with TMAB or with $NaBH_4$ (alkyl and aralkyl derivatives) were cleaved to an

---

(*) Compounds IIb where R was phenyl and benzyl were prepared, while our work was in progress by Magnien et al. (3) through the same way. These Authors however ascribe to the starting products an azomethine structure. The N.M.R. spectra, (which were kindly recorded and interpreted by Dr. A.MELERA of VARIAN AG Zurich) of some I chosen among compounds reacting and not reacting with reduction agents, induced us to conclude that the usually accepted cyclic structure is to be preferred.

extent of about 30%, while the decomposition of aryl derivatives ranged from 50 to 90%.

A parallel behaviour was observed by weighing the dinitrophenylhydrazones of the aldehydes (VI) precipitated by letting compounds Ia at room temp. for 16 hr. in an acid solution of excess dinitrophenylhydrazine. The precipitation of the phenylhydrazone did not take place in the alkylderivatives, it took place to an extent of about 30% in the benzyl derivative and to about 100% in the arylderivatives.

A similar behaviour was shown in the dihydroquinazolones, where the precipitation of the theoretical amount of the dinitrophenylhydrazone took place only in the compounds which reacted with TMAB.

All Ib were very easily cleaved by dinitrophenylhydrazine, with almost quantitative yields, whatever R might be. This could explain the better yields of IIb and IIc obtained.

This cleavage of the heterocyclic ring of arylsubstituted dihydrochlorothiazides with $NaBH_4$ can provide a new method for synthesizing the monosubstituted disulfonamides IIa.

REFERENCES

(1) J.G.TOPLISS, M.H.SHERLOCK, F.H.CLARCKE, M.C.DALY, B.W.PETTERSEN, J.LIPSKI and N.SPERBER - J.Org.Chem. 26, 3824 (1961).

(2) C.W.WHITEHEAD and J.J.TRAVERSO - J.Org.Chem. 27, 951 (1962)

(3) E.MAGNIEN, W.TOM and W.OROSHNIK - J.Med.Chem. 7, 821 (1964).

(4) T.A.KILROE SMITH and H.STEPHEN - Tetrahedron 1, 38 (1957).

(5) C.R.REHM and J.B.SMITH - J.Am.Pharm.Ass. 49, 386 (1960).