REACTION OF 8-CHLORO-10,11-DIHYDRODIBENZO[*b,f*]THIEPIN-10-ONE WITH AROMATIC ALDEHYDES

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Dedicated to Professor F. Šantavý on the occasion of his 60th birthday.

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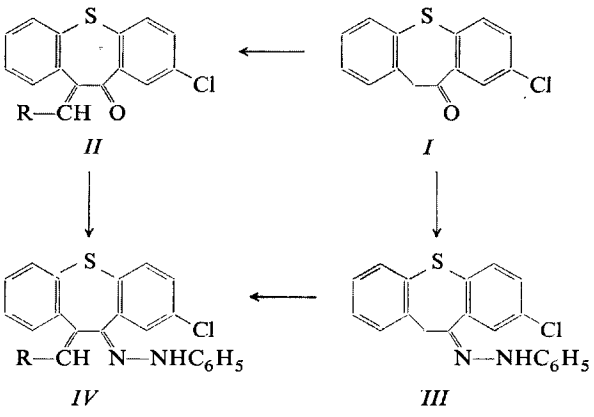
Reaction of 8-chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-one (*I*) with benzaldehyde, 4-chlorobenzaldehyde, and 4-dimethylaminobenzaldehyde in a boiling mixture of pyridine, ethanol, and a little piperidine affords the corresponding 11-arylidene derivatives *IIa,b,c*. Products *IIa,b* (but not *IIc*) are also obtained by the mixed aldolisation of compound *I* with the appropriate aromatic aldehyde. The phenylhydrazone *III* (obtained by reaction of compound *I* with phenylhydrazine) reacts in a boiling mixture of pyridine, ethanol, and piperidine only with benzaldehyde to afford the benzylidene derivative *IVa*.

In connection with investigations on psychotropic substances from the dibenzo[*b,f*]thiepine group, there has been examined reactivity of hydrogen atoms in the methylene group at position 11 of 8-chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-one (*I*) which is the key intermediate in the synthesis of the Czechoslovak neuroleptic Clothepine, *i.e.*, 8-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo-[*b,f*]-thiepine[1-4]. The reactivity was tested by means of an analogy of the Doebner reaction and by the mixed aldolisation. Benzaldehyde, 4-chlorobenzaldehyde, and 4-dimethylaminobenzaldehyde were used as reactants. By reaction of these aldehydes with 8-chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-one (*I*) in a boiling mixture of pyridine, ethanol, and a little piperidine, there were obtained the corresponding 11-arylidene derivatives *IIa,b,c* in fair yields. Aldolisation of compound *I* with benzaldehyde and *p*-chlorobenzaldehyde in aqueous-ethanolic sodium hydroxide at a moderately elevated temperature yielded identical 11-arylidene derivatives *IIa,b* resp. On the other hand, *p*-dimethylaminobenzaldehyde does not react with compound *I* under such conditions. The condensation thus proceeds more readily under conditions of the Doebner synthesis than under aldolisation conditions. The removal of water from the primary aldolisation product with the formation of a double bond at position 11 can be reasonably assumed since the β-elimination

is facilitated by the presence of a carbonyl group at position 10 and a wide mesomerism of dibenzo[*b*,*f*]thiepinone system.

In another paper[5], we have examined the analogy of the Doebner synthesis in the case of 5,6-dihydro-6-azauracil (hexahydro-1,2,4-triazine-3,5-dione), *i.e.*, on the methylene group of the —CO—CH_2—NH— type. To elucidate the effect of additional groups on the reactivity of the methylene group, 8-chloro-10-phenylhydrazono-10,11-dihydrodibenzo[*b*,*f*]thiepine (*III*) was used as the model compound. When compound *III* (prepared by reaction of compound *I* with phenylhydrazine in the medium of ethanol and a small amount of acetic acid) is refluxed with benzaldehyde in a mixture of pyridine, ethanol, and a little piperidine, there is obtained 8-chloro--11-benzylidene-10-phenylhydrazono-10,11-dihydrodibenzo[*b*,*f*]thiepine (*IVa*) which is also formed by reaction of the benzylidene derivative *IIa* with phenylhydrazine.



a, R = C_6H_5
b, R = 4-ClC_6H_4
c, R = 4-$(CH_3)_2NC_6H_4$

Compound *III* does not react with 4-chlorobenzaldehyde or 4-dimethylaminobenzaldehyde under the Doebner conditions. As expected, compound *III* also does not react with any of the above three aromatic aldehydes under conditions of the mixed aldolisation reaction. Replacement of the carbonyl group oxygen atom by the hydrazone group nitrogen atom obviously results in such a decrease of the reactivity of the vicinal methylene group that (in accordance with the lower electronegativity of the nitrogen atom) the Doebner reaction takes place with more reactive aromatic aldehydes only. The above reported reactions make possible to introduce suitable substituents into position 10 and 11 of the 10,11-dihydrodibenzo[*b*,*f*]thiepin-10-one system and thus prepare novel derivatives.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). Analytical samples were dried at 60° C/20 Torr for 5 h.

Condensation of 8-Chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-2-one (*I*) with Aromatic Aldehydes

A. *Under conditions of the Doebner reaction.* A mixture of compound *I* (2·61 g; 0·01 mol), the appropriate aldehyde, pyridine (25 ml), ethanol (25 ml), and piperidine (5 ml) was refluxed for 6 h, the resulting solution evaporated to dryness under diminished pressure, the residue co-evaporated with two 25 ml portions of ethanol, and finally recrystallised from ethanol. With the use of benzaldehyde (5 ml), there was obtained 2·6 g (75%) of 8-chloro-11-benzylidene-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-one (*IIa*), m.p. 144—146°C. For $C_{21}H_{13}ClOS$ (349·4) calculated: 72·30% C, 3·76% H, 10·17% Cl, 9·19% S; found: 72·01% C, 3·74% H, 10·05% Cl, 9·08% S. From 4-chlorobenzaldehyde (1·55 g; 0·011 mol), there was obtained 3·16 g (82%) of 8-chloro-11-(4-chlorobenzylidene)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-one (*IIb*), m.p. 168—170°C. For $C_{21}H_{12}Cl_2OS$ (383·0) calculated: 65·80% C, 3·13% H, 18·50% Cl, 8·35% S; found: 65·50% C, 3·09% H, 18·41% Cl, 8·25% S. With the use of 4-dimethylaminobenzaldehyde (1·63 g; 0·011 mol), there was obtained 3·20 g (81%) of 8-chloro-11-(4-dimethylaminobenzylidene)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-one (*IIc*), m.p. 204—206°C. For $C_{23}H_{18}ClNOS$ (391·5) calculated: 70·50% C, 4·60% H, 9·06% Cl, 3·58% N, 8·18% S; found: 70·39% C, 4·51% H, 9·12% Cl, 3·45% N, 8·21% S.

B. *Under conditions of the mixed aldolisation.* A mixture of compound *I* (2·61 g; 0·01 mol), the appropriate aldehyde, and ethanol (95 ml) was dissolved at 35°C and then a solution of sodium hydroxide (0·88 g; 0·022 mol) in water (50 ml) was added. The whole mixture was stirred at 35°C for 3 h and at room temperature for additional 3 h to deposit a solid which was collected with suction, washed with water until neutral, and recrystallised from ethanol. With the use of benzaldehyde (2·12 g; 0·02 mol), there was obtained 2·74 g (78%) of compound *IIa*, m.p. 144—146°C, undepressed on admixture with the specimen obtained by procedure *A*. From 4-chlorobenzaldehyde (1·55 g; 0·011 mol), there was obtained 3·02 g (79%) of compound *IIb*, m.p. 168—170°C, undepressed on admixture with the specimen obtained by procedure *A*.

8-Chloro-10-phenylhydrazono-10,11-dihydrodibenzo[*b*,*f*]thiepine (*III*)

A mixture of compound *I* (2·61 g; 0·01 mol), phenylhydrazine (1·18 g; 0·011 mol), ethanol (50 ml), and acetic acid (2 ml) was refluxed for 2 h, evaporated under diminished pressure, and the residue crystallised from ethanol (50 ml) to afford 2·75 g (78·5%) of compound *III*, m.p. 140—142°C. For $C_{20}H_{15}ClN_2S$ (350·5) calculated: 68·50% C, 4·28% H, 10·13% Cl, 8·00% N, 9·15% S; found: 68·37% C, 4·24% H, 10·25% Cl, 8·15% N, 9·03% S.

8-Chloro-11-benzylidene-10-phenylhydrazono-10,11-dihydrodibenzo[*b*,*f*]thiepine (*IVa*)

A. A mixture of compound *III* (1·75 g; 0·005 mol), benzaldehyde (3 ml), pyridine (15 ml), ethanol (15 ml), and piperidine (3 ml) was refluxed for 6 h, the resulting solution evaporated under diminished pressure, and the residue crystallised from 90% aqueous ethanol (250 ml) to afford 1·8 g (82%) of compound *IVa*, m.p. 252—259°C (decomp.). For $C_{27}H_{19}ClN_2S$ (438·5) calculated: 74·00% C, 4·34% H, 8·10% Cl, 6·40% N, 7·32% S; found: 73·92% C, 4·31% H, 8·05% Cl, 6·32% N, 7·21% S.

B. A mixture of compound *IIa* (1·74 g; 0·005 mol), phenylhydrazine (1·18 g; 0·011 mol), ethanol (30 ml), and acetic acid (2 ml) was refluxed for 2 h, the resulting solution evaporated under diminished pressure, and the residue crystallised from ethanol (250 ml) to afford 1·81 g (83%) of compound *IVa*, m.p. 253—259°C (decomp.), undepressed on admixture with the specimen obtained by procedure *A*.

REFERENCES

1. Protiva M., Jílek J. O., Metyšová J.: Czechoslov. Pat. 124 533 (1967).
2. Protiva M., Jilek J. O., Metyšová J., Ernest I., Pelz K., Adlerová E.: Czechoslov. Pat. 121 337 (1966), US-Pat. 3 351 599 (1966). Spofa: Neth. Appl. 6 517 282 (1966); Chem. Abstr. *66*, 2591 (1967).
3. Protiva M., Jílek J. O., Metyšová J., Seidlová V., Jirkovský I., Metyš J., Adlerová E., Ernest I., Pelz K., Pomykáček J.: Farmaco (Pavia) Ed. Sci. *20*, 721 (1965); Chem. Abstr. *64*, 5090 (1966).
4. Jílek J. O., Metyšová J., Pomykáček J., Protiva M.: This Journal *33*, 1831 (1968).
5. Nováček A., Gut J.: This Journal, in press.

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