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Benzothiazolo[3,2—*c*]-1,3-dioxolo[4,5—*g*]quinazolines

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Some 5,12a-dihydro-6-alkyl/aryl-6*H*-benzothiazolo[3,2—*c*]-1,3-dioxolo [4,5—*g*]quinazolines with *cis* as well as *trans* stereochemistry of the hydrogens at carbon 6 and 12a have been synthesised. The synthesis of another series of compounds of the above system with thiazole ring at position 6 has also been accomplished. The structures have been established on the basis of IR and PMR data.

(Keywords: Heterocycles; ^{1}H-*NMR; Stereochemistry; Synthesis)*

Benzothiazolo[3,2—c]-1,3-dioxolo[4,5—g]chinazoline

Es wurde eine Reihe von 5,12a-Dihydro-6-alkyl/aryl-6*H*-benzothiazolo [3,2—*c*]-1,3-dioxolo[4,5—*g*]chinazoline, sowohl mit *cis*- als auch *trans*-ständigen Wasserstoffatomen an Kohlenstoff 6 und 12a, synthetisiert. Ebenso wurden auch Verbindungen dieses Systems mit Thiazol an Position 6 hergestellt. Die Strukturen wurden mittels IR- und NMR-spektroskopischen Daten abgesichert.

In order to evolve new ystems with probable activity around the general pattern of drugs already known in the literature, we wish to report here the synthesis of some 5,12a-dihydro-6-alkyl/aryl-6*H*-benzothiazolo[3,2—*c*]-1,3-dioxolo[4,5—*g*]quinazolines.

Condensation of *o*-aminopiperonal (**1**) and *o*-aminothiophenol hydrochloride (**2**) resulted in the formation of 2-(2′-amino-4′,5′-methylenedioxyphenyl)benzothiazolidine (**3**). The structure of **3** has been confirmed on the basis of IR and its solubility behaviour.

A sharp IR absorption band originally present in *o*-aminopiperonal (**1**) at 1,650 cm^{-1} (CHO) and a sharp IR stretching absorption band originally present in *o*-aminothiophenol hydrochloride (**2**) at 2,545 (C—SH) were absent in **3**. Furthermore the condensation product was insoluble in sodium hydroxide indicating thereby the absence of —SH group. **3** was converted into its hydrochloride **3a** by passing dry hydrochloric acid through its cold ethereal suspension.

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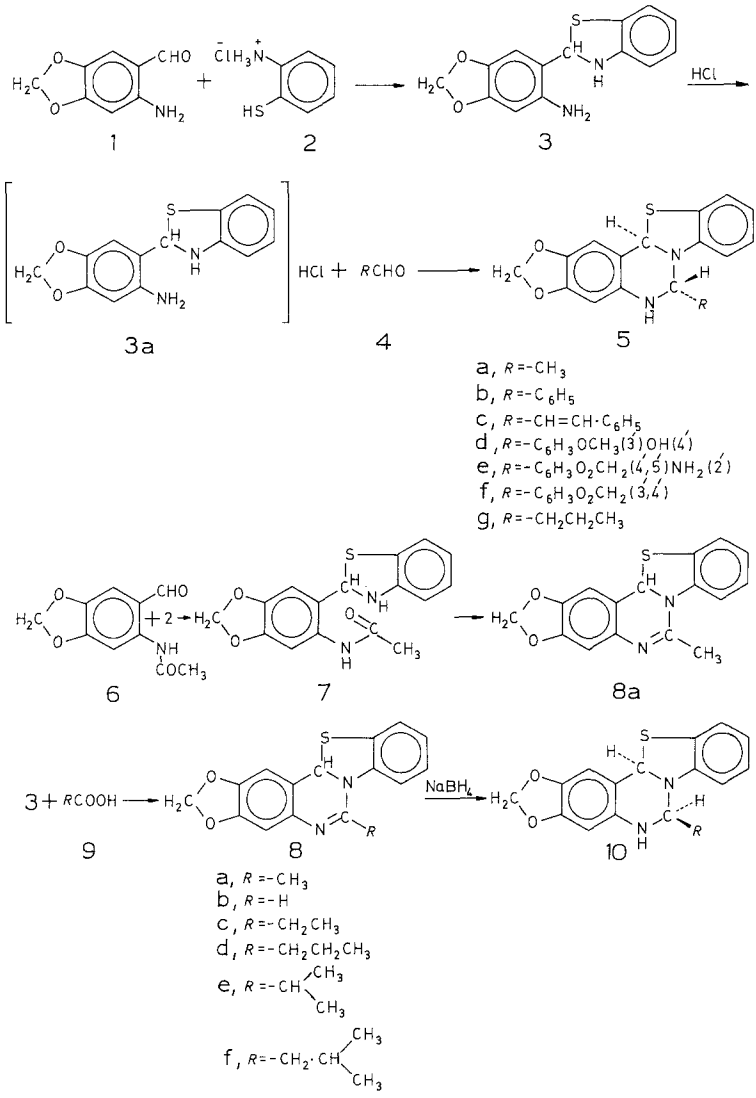
Scheme 1



On condensation of **3** with various aldehydes **4**, cyclodehydration occurred with the formation of 5,12a-dihydro-6-substituted-6*H*-benzothiazolo[3,2—*c*]-1,3-dioxolo[4,5—*g*]quinazolines (**5**). The structure of **5** has been confirmed on the basis of elemental analysis and PMR studies.

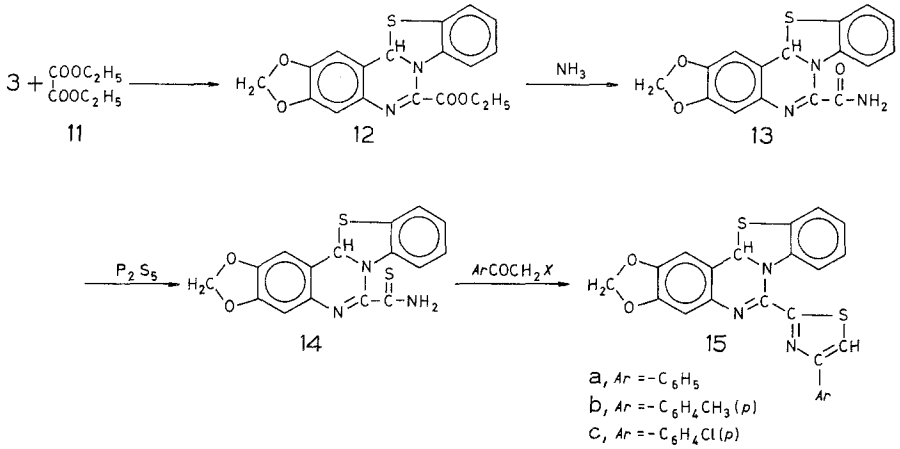
An attempt was made to prepare **5** by an alternative route: Condensation of acetamidopiperonal (**6**) with *o*-aminothiophenol resulted in the formation of uncyclised intermediate **7**. The latter upon cyclisation with $POCl_3$ and PCl_3 resulted in the formation of 6-methyl-12a*H*-benzothiazolo[3,2—*c*]-1,3-dioxolo[4,5—*g*]quinazoline (**8a**), a product which was also obtained by the condensation of **3** with acetic acid. The structure of **8a** has again been confirmed on the basis of analytical results and absence of IR band at 1,690 present originally in **7**. **8a** upon reduction with sodium borohydride gave the product **10a** which was different from the product obtained by the condensation of **3** with acetaldehyde.

This led to the conclusion that the two products differ in their stereochemistry at positions 6 and 12a. Models reveal that if the hydrogens at position 6 and 12a are in *trans* position, then methyl group at position 6 comes close to the benzene ring and hence should absorb slightly downfield whereas the H atom at position 6 is in axial position, away from the benzene ring and should absorb at a normal value. But if the two H atoms are in *cis* position, then the methyl group in position 6 is in axial position away from the benzene ring and should absorb at the normal value whereas the H atom at position 6 which is in an equatorial position comes close to the benzene ring and should absorb downfield. On this basis it could be established that the product obtained by the condensation of acetaldehyde with 2-(2′-amino-4′,5′-methylenedioxy phenyl)benzothiazolidine which besides other PMR signals gave a doublet (3H) at 1.72 (CH—C**H**$_3$) and a multiplet (1H) at 3.90 (C**H**—CH_3) has *trans* hydrogens at C-6 and C-12a, whereas the latter one i.e. the one obtained after reduction with sodium borohydride, which besides other signals, gave a doublet (3H) at 1.37 (CH—C**H**$_3$) and a multiplet (1H) at 5.14 (C**H**—CH_3) has *cis* hydrogens at C-6 and C-12a (values in δ/ppm). Further work in this field is in progress.

In another series the thiazole ring in position 6 of the parent ring has been introduced. In this case, cyclisation of **3** was accomplished with an ester instead of an aldehyde or an acid. Thus **3** on condensation with diethyloxalate resulted in the formation of an ester **12**. Its structure was established on the basis of analytical results and IR studies. An IR absorption band occurs at 1,705 due to (N=C—$COOC_2H_5$) and at 1,620 due to (C=N). **12** on treatment with liquid ammonia gave carboxamide derivative **13** which gave its characteristic IR absorption band at 1,675 due to amidic and at 3,400-3,100 due to N—H stretching (—CO—NH_2). The carboxamide derivative was treated with P_2S_5 in pyridine to yield the thiocarboxamide derivative **14** whose structure has again been confirmed on the basis of IR. **14** exhibits its characteristic IR absorp-

tion band at 3,400-3,150 due to (N—H) stretching but the band at 1,675 present in carboxamide disappeared showing the conversion of —CO—NH_2 to CS—NH_2. **14** upon treatment with haloketones gave the desired benzothiazolo [3,2—*c*]-1,3-dioxolo[4,5—*g*]quinazolines with thiazole substitution in position 6 (**15**). **15** showed an IR band at 1,610 due to (C=C). No IR band appeared in the range 3,400-3,000 due N—H stretching or 1,720-1,670 due to C=O indicating thereby the cyclic structure at position 6.

Scheme 2



Experimental

Melting points were determined in open glass capillaries using liquid paraffin bath and are uncorrected. IR spectra were recorded in nujol on Perkin-Elmer 337 and PMR on Varian EM-390 90 MHz spectrometer using *TMS* as the internal reference.

o-Aminothiophenol hydrochloride (**2**)

A slow stream of dry hydrochloric acid was passed through well-cooled ethereal solution of *o*-aminothiophenol (5 g), for 1 h with continuous stirring. A white solid thus separated, was filtered under suction and washed with dry ether, m.p. 216° (reported 217°)[1]; yield being 5,5 g.

2-(2'-Amino-4',5'-methylenedioxyphenyl)benzothiazolidine (**3**)

To a solution of *o*-aminopiperonal[2] (**1**) (1.65 g, 0.01 mol) in ethanol (15 ml) were added fused sodium acetate (0.82 g, 0.01 mol) and *o*-aminothiophenol hydrochloride (**2**) (1.61 g, 0.01 mol). The contents were heated with vigorous shaking and then refluxed on a steam bath for 0.5 h. A yellow solid thus separated was filtered under suction, washed with water and crystallised from ethanol into yellowish needles, m.p. 176°; yield 1.4 g (51%).

IR (in nujol): 3,440-3,350 (b), 3,270, 1,610, 1,280, 1,230, 1,105, 1,070, 1,040, 948, 845, and 750 cm^{-1}.

2-(2'-Amino-4',5'-methylenedioxyphenyl)benzothiazolidine hydrochloride (**3 a**)

2 g of **3** were suspended in well-cooled dry ether (150 ml). Through this dry hydrochloric acid was bubbled for 2 h. A new solid thus separated, was filtered under suction and crystallised from ethanol into brownish plates, m.p. 196° d; yield 2.1 g (83%).

5,12a-Dihydro-6-methyl-6H-benzothiazolo[3,2—c]-1,3-dioxolo[4,5—g]quinazoline (**5**)

Fused sodium acetate (0.82 g, 0.01 mol) was added to a solution of **3 a** (3.08 g, 0.01 mol) in ethanol (50 ml). To this freshly distilled acetaldehyde (0.44 g, 0.01 mol) dissolved in the same solvent (5 ml) was added. After keeping at room temperature for 1 h, the contents were refluxed on a steam bath (with continuous bubbling of dry nitrogen gas). There was separation of a new solid after 1 h. Refluxing was continued for another 2 h to complete the reaction. It was cooled to room temperature, filtered under suction, washed with water and crystallised from ethanol into brown needles, m.p. 172°; yield 2.53 g (85%).

IR (in nujol): 3,400-3,300, 1,610, 1,240, 1,165, 1,040, 940, 870, 790, and 760 cm^{-1}.

Other aldehydes were also condensed with **3 a** under identical conditions. The data, regarding yield, solvent for crystallisation, m.p., and molecular formula are tabulated in Table 1.

2-(2'-Acetamido-4',5'-methylenedioxyphenyl)benzothiazolidine (**7**)

A solution of freshly distilled *o*-aminothiophenol (**2**) (1.25 g, 0.01 mol) in dry dimethylformamide (5 ml) was added to a solution of acetamidopiperonal (**6**)[2,3] (2.07 g, 0.01 mol) in 20 ml of the same solvent. The contents were refluxed in an

Table 1. *5,12a-Dihydro-6-substituted-6H-benzothiazolo[3,2—c]-1,3-dioxolo-[4,5—g]quinazolines* (**5**)

Compd. No. **5**	*R*	m.p.[a] °C	Yield %	Molecular formula[b]
a	Methyl	172	85	$C_{16}H_{14}N_2O_2S$
b	Phenyl	218	90	$C_{21}H_{16}N_2O_2S$
c	Cinnamyl	310	86	$C_{23}H_{18}N_2O_2S$
d	4'-Hydroxy-3'-methoxyphenyl	228	80	$C_{22}H_{18}N_2O_4S$
e	2'-Amino-4',5'-methylenedioxyphenyl	220	85	$C_{22}H_{17}N_3O_4S$
f	3',4'-Methylene-dioxyphenyl	255	76	$C_{22}H_{16}N_2O_4S$
g	*n*-Propyl	210	72	$C_{18}H_{18}N_2O_2S$

[a] All compounds were crystallised from ethanol.
[b] C,H,N values agree with the proposed structures.

oil bath for 5 h. On cooling a greenish yellow crystalline compound separated out. It was filtered under suction and crystallised from dioxane into light greenish yellow needles, m.p. 210°; yield 1.6 g (51%).

IR (in nujol): 3,155, 3,040, 1,690, 1,635, 1,565, 1,490, 1,420, 1,390, 1,310, 1,290, 1,265, 1,215, 1,185, 1,100, 1,080, 1,045, 1,010, 960, 930, 875, 850, 750, and 720 cm^{-1}.

6-Methyl-12aH-benzothiazolo[3,2—c]-1,3-dioxolo[4,5—g]quinazoline (**8a**) (via **7**)

7 (3.14 g, 0.01 mol) was added to a mixture of freshly distilled phosphorus oxychloride (5 ml) and phosphorus trichloride (5 ml) at room temperature with continuous stirring. After keeping at room temperature for 0.5 h, the contents were heated on a steam bath. A clear solution was obtained after 20 min, followed by immediate separation of a new compounds. Heating was continued for another 15 min to ensure completion of reaction. The contents were cooled to room temperature and poured on crushed ice (100 g). The solid thus separated was filtered under suction, washed with water and crystallised from ethanol into light yellow plates, m.p. 200°; yield 1.8 g (61%).

IR (in nujol): 1,625, 1,540, 1,320-1,310, 1,270, 1,220, 1,190, 1,110, 1,050, 870, 790, 760, and 720 cm^{-1}.

6-Methyl-12aH-benzothiazolo[3,2—c]-1,3-dioxolo[4,5—g]quinazoline (**8a**) (via **3**)

3 (1 g) was taken in excess of acetic acid (20 ml). The reaction mixture was refluxed on an oil bath. Progress of reaction was monitored by carrying out tlc at regular intervals. Refluxing was continued over 6 h. After removing the excess of acetic acid under vacuum, a sticky solid thus obtained was treated with dilute solution of sodium carbonate and finally washed with water. It was purified either by passing it through a column containing activated neutral alumina (elution by pure ether) or crystallising it from ethanol, m.p. 200°.

Other acids were also condensed with 2-(2′-amino-4′,5′-methylenedioxyphenyl)benzothiazolidine to get their respective analogues. Data regarding m.p., yield, mode of purification, molecular formula, and IR are tabulated in Table 2.

5,12a-Dihydro-6-methyl-6H-benzothiazolo[3,2—c]-1,3-dioxolo[4,5—g]quinazoline (**10a**)

Sodium borohydride (0.304 g, 0.008 mol) was added to a solution of **8a** (0.296 g, 0.001 mol) in ethanol (80 ml). The contents were gently heated at 50-60° for 1 h and finally refluxed over a steam bath for 10 h. After complete evaporation of ethanol, water (20 ml) was added to it and the solid thus separated was collected under suction. The crude product was crystallised from ethanol. The first crystallised crop was found to be unreacted **8a** on the basis of m.p., m.m.p., tlc and IR. On evaporating the filtrate, the solid thus obtained was crystallised from ethanol into light yellow plates of the desired reduced product **10a** with m.p. 158° in 60% yield.

IR (in nujol): 3,450-3,350, 1,620, 1,285, 1,235, 1,110, 1,072, 1,048, 950, 875, 848, 752, and 730 cm^{-1}.

6-Carbethoxy-12aH-benzothiazolo[3,2—c]-1,3-dioxolo[4,5—g]quinazoline (**12**)

3 (2.72 g, 0.01 mol) and diethyloxalate (**11**) (2.92 g, 0.02 mol) were mixed thoroughly. The contents were heated under reflux at 180° in an oil bath under

Table 2. *6-Substituted-12aH-benzothiazolo[3,2—c]-1,3-dioxolo[4,5—g]quinazolines* (**8**)

Compd. No. **8**	*R*	m.p., °C	Yield (%)	Mode of purification	Molecular formula	IR (cm^{-1})
a	CH_3	200	76	Crystallisation (ethanol) or column chromatography (ether)	$C_{16}H_{12}N_2O_2S$	1,635, 1,555, 1,330, 1,310, 1,265, 1,220, 1,195, 1,115, 1,040, 970, 955, 950, 880, 790, 765, 730
b	H	184	80	Crystallisation (dioxane)	$C_{15}H_{10}N_2O_2S$	1,625, 1,550, 1,480, 1,300, 1,240, 1,215, 1,180, 1,170, 1,090, 1,070, 1,040, 955, 930, 885, 825, 770, 740, 710
c	CH_2CH_3	153-154	65	Crystallisation (ethanol) or column chromatography (50% pet. ether, 50% ether)	$C_{17}H_{14}N_2O_2S$	1,620, 1,550, 1,280, 1,260, 1,225, 1,110, 1,070, 1,045, 960, 870, 760, 730
d	$CH_2CH_2CH_3$	150-151	60	Column chromatography (50% pet. ether, 50% ether)	$C_{18}H_{16}N_2O_2S$	1,610, 1,560, 1,3 0, 1,260, 1,240, 1,215, 1,175, 1,100, 1,080, 1,045, 960, 935, 875, 775, 745, 725
e	$CH(CH_3)_2$	162	60	Column chromatography (50 % pet. ether, 50% ether)	$C_{18}H_{16}N_2O_2S$	1,625, 1,550, 1,312, 1,290, 1,270, 1,235, 1,195, 1,120, 1,095, 1,048, 965, 870, 780, 760, 750, 730
f	$CH_2CH(CH_3)_2$	150	55	Column chromatography (50% pet. ether, 50% ether)	$C_{19}H_{18}N_2O_2S$	1,625, 1,560, 1,310, 1,280, 1,265, 1,210, 1,110, 1,090, 1,070, 1,040, 955, 935, 870, 820, 770, 720

nitrogen atmosphere with continuous stirring for 6 h. After cooling, the excess of diethyl oxalate was removed by triturating with petroleum ether. The crystalline solid thus separated was filtered under suction and crystallised from glacial acetic acid into orange brown plates, m.p. 218°; yield 2.34 g (66%).

IR (in nujol): 1,705, 1,620, 1,310, 1,282, 1,240, 1,218, 1,165, 1,105, 1,042, 1,020, 960, 930, 850, 750, and 725 cm^{-1}.

12a H-Benzothiazolo[3,2—c]-1,3-dioxolo[4,5—g]quinazolin-6-carboxamide (**13**)

2.0 g **12** suspended in well cooled absolute ethanol (200 ml) was saturated with liquid ammonia. After keeping overnight, the separated solid was filtered under suction and crystallised from ethanol into cream coloured plates, m.p. 275°; yield 1.1 g (60%).

IR (in nujol): 3,400-3,100, 1,675, 1,615, 1,550, 1,290, 1,240, 1,210, 1,090, 1,045, 955, 870, 750, and 720 cm^{-1}.

12aH-benzothiazolo[3,2—c]-1,3-dioxolo[4,5—g]quinazolin-6-thiocarboxamide (**14**)

Phosphorus pentasulphide (1.5 g) was added to a solution of 1 g **13** in dry pyridine (20 ml) at room temperature. The reaction mixture was refluxed in an oil bath for 4–5 h. It was cooled to room temperature and poured on crushed ice (100 g) followed by acidification with glacial acetic acid, with continuous stirring. A dark brown crystalline mass thus separated, was filtered under suction, washed with ice cold water and crystallised from ethanol, m.p. 203°; yield 0.52 g (50%).

IR (in nujol): 3,400-3,150 —C(S)NH_2, 1,615 (C=N—) cm^{-1}.

6-[2'-(4'-Phenylthiazolo)]12aH-benzothiazolo[3,2—c]-1,3-dioxolo[4,5—g]-quinazoline (**15a**)

A solution of α-bromoacetophenone[4] (0.5 g, 0.0025 mol) in absolute ethanol (15 ml) was added to a solution of **14** (0.85 g, 0.0025 mol) in 350 ml of the same solvent. The contents were refluxed over steam bath for 10 h. On cooling, a solid thus separated, was filtered under suction and crystallised from ethanol into dark brown needles, m.p. 241°; yield 0.62 g (56%).

IR (in nujol): 1,610, 1,260, 1,190, 1,105, 1,040, 940, and 750 cm^{-1}.

14 on condensation with α-chloro-p-methyl acetophenone[5] furnished **15 b** in 48% yield, m.p. > 300° (ethanol).

Similarly **14** on condensation with α-p-dichloroacetophenone[6] furnished **15 c** in 46% yield, m.p. > 300° (ethanol).

IR (in nujol): 1,610, 1,270, 1,240, 1,210, 1,160, 1,100, 1,040, 950, 850, 760, and 725 cm^{-1}.

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