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Potential Biologically Active Agents, XXVII[1]:

Synthesis of Some 4-Substituted Phenylmercaptoacetic Acids

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Condensation of 4-(3*H*)-quinazolinone (**2**) with 4-(aminophenyl)-mercaptoacetic acid under the conditions of the Mannich reaction furnished compounds **3a** and **3b**. Reaction of **4** with 4-(amino-phenyl)mercaptoacetic acid yielded **5** which when treated with aryl aldehydes gave **6**. Similarly, compounds **8** were obtained from **7**.

Potentiell biologisch aktive Verbindungen, 27. Mitt.[1]

Die Synthese einiger 4-substituierter Phenylmercaptoessigsäuren

Die Kondensationen von 4-(3*H*)-Chinazolinon (**2**) mit 4-Amino-phenylmercaptoessigsäure unter den Bedingungen der Mannich Reaktion lieferte **3a** und **3b**. Die Reaktion von **4** mit 4-Aminophenyl-mercaptoessigsäure ergab **5**, das mit Arylaldehyden **6** ergab; ähnlich wurde **8** aus **7** dargestellt.

Quinazolones are reported to possess good central nervous system depressant properties[2]. Some 2,3-disubstituted quinazolones were investigated[3)4)] and it was found that 2-methyl-3-o-tolyl-4-quinazolone is a potent anticonvulsant drug [5]. γ-Aminobutyric acid (GABA) is considered as a central inhibitory neuroharmonal modulator[6] and some carboxylic acids have been reported to possess significant anticonvulsant properties[7]. It was speculated that the presence of a carboxylic group in the substituted quinazolones might result in better anticonvulsant activity. These observations led us to synthesis few substituted 2-methyl-(phenyl and styryl)-3-[4(3*H*)-quinazolyl]-phenyl-4-mercapto-acetic acids and related compounds for pharmacological screening.

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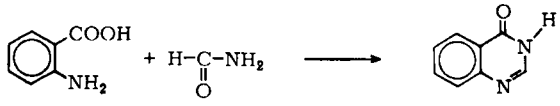
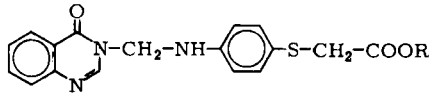
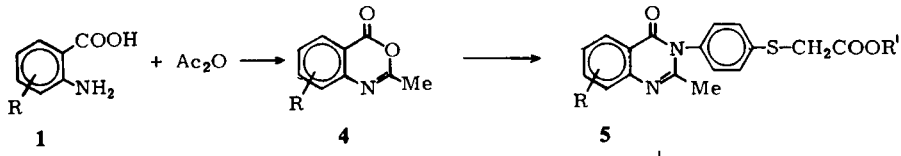


1 **2**

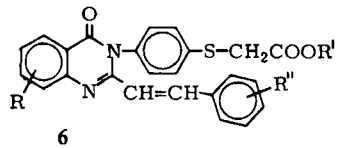


3 **a:** R = H
b: R = Me



1 **4** **5**

a: R = H
b: R = 6-Br
c: R = 6,8-diBr



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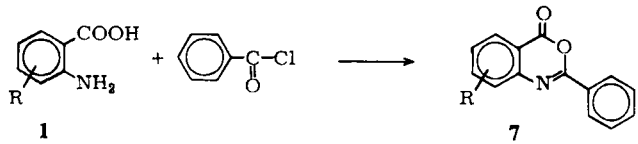
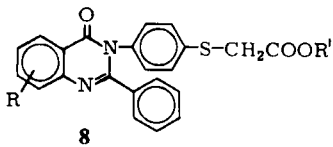


1 **7**



8

Experimental

3-[4-(3H)-Quinazolyl]k-methyl-4'-aminophenylmercaptoacetic acid **(3a)**

A mixture of 1.46 g (0.01 mole) **2**[8)9)], 1,5 ml formalin and 1.83 g (0.01 mole) 4-aminophenylmercaptoacetic acid were taken in 25 ml ethanol. The reaction mixture was heated on a water bath with stirring for 10 min. It was then allowed to stand at room temp. overnight. The solid mass thus deposited was recrystallised from methanol, yield 60 %, m. p. 163–164°. $C_{17}H_{15}N_3O_3S$ (341.3) Calcd.: N 12.3 -Found: N 12.1.

Methyl-3-[4-(3H)-quinazolyl]-methyl-4'-aminophenylmercaptoacetate **(3b)**

It was similarly obtained from **2** and methyl-4-aminophenyl-mercapto acetate and recrystallised from methanol, yield 75 %, m. p. 112°. ^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.35 (CH_2), 3.43 (Me), 5.30 (N-CH_2-N), 6.5–8.2 (H-aromatic). $C_{18}H_{17}N_3O_3S$ (355.4) Calcd.: N 11.8 Found: 11.5

3-[2-Methyl-4-(3H)-quinazolyl]-phenyl-4'-mercaptoacetic acids **(5)** (Table 1)

A mixture of 2.5 ml acetic anhydride and 1.37 g anthranilic acid was refluxed for 1 h. Excess of acetic anhydride was distilled off and the crude **4a** thus obtained was mixed with 1.83 g 4-aminophenylmercaptoacetic acid. The resulting mixture was heated in an oil bath at 170° for 30 min. The reaction mixture was cooled and it was left overnight after addition of 5 ml methanol. The solid product thus separated was recrystallised from ethanol.

3-[2-Styryl-4-(3H)-quinazolyl]phenyl-4'-mercaptoacetic acids **6** (Table 2)

To a refluxing solution of 1.63 g (5 mmole) **5a** in 15 ml glacial acetic acid 0.6 g (5 mmole) salicylaldehyde was added. The reaction mixture was heated under reflux for 8 h. The crude product thus deposited on cooling was recrystallised from excess of acetic acid, yield 60 %, m. p. >272°.

2-[Phenyl-4-(3H)-quinazolyl]-phenyl-4'-mercaptoacetic acids **8** (Table 3)

They were prepared by the method of *Samour* et al.[10] 1.37 g Anthranilic acid were taken in 2.5 ml pyridine and 2.8 ml benzoyl chloride was added to it in portions with shaking. The reaction mixture was kept for 30 min at room temp. and then it was treated with 10 % sodium hydrogencarbonate to remove unreacted acid. Finally it was washed with water and recrystallised from benzene-petrolether (60–80°), yield 70 %, m.p. 121–122° (Lit.[10] m.p. 123°). **7** thus obtained were used for the preparation of **8**. 2.22 g **7** (R = H, 0.01 mole) and 2.26 g 4-aminophenylmercaptoacetic acid (0.012 mole) were taken in 10 ml pyridine and 5 ml water. The reaction mixture was heated under reflux for 5 h. After the completion of the reaction the excess of pyridine and water were distilled off and the residue was digested with 100 ml N-HCl for 2 h on a water bath. The separated solid **8a** was recrystallised from benzene-petrolether (60–80°), yield 50 %, m.p. 165°.

Methyl-(4-aminophenylmercapto)-acetate

10 g 4-aminophenylmercaptoacetic acid were taken in 100 ml absol. methanol. The mixture was cooled in ice and 10 ml of thionyl chloride were added to it dropwise. The reaction mixture was refluxed for 10 h. Excess of methanol was distilled off; the residue was neutralised with 10 % $NaHCO_3$ and then it was extracted with ether, the ether extract was washed with water and dried ($MgSO_4$). The syrupy aminoester having dark brown colour was obtained after removal of ether. A small amount of this ester was taken in ether und dry HCl gas was passed into it. The resulting white solid was recrystallised from methanol, white crystals, m. p. 166–170° (Lit.[11] m. p. 168–177°).

Table 1: *3-[2-Methyl-4-(3H)-quinazolyl]-phenyl-4-'mercaptoacetic acids* **5**

Compound No.	R	R'	Yield %	M.P. °C	Molecular formula (Mol.wt.)	Calcd. Found N
5a	H	H	45	263–264	$C_{17}H_{14}N_2O_3S$ (326.3)	8.6 8.7
5b*	H	Me	60	215–216	$C_{18}H_{16}N_2O_3S$:HCl (376.8)	7.4 6.7
5c	7-NO_2	H	45	230	$C_{17}H_{13}N_3O_5S$ (371.3)	C: 55.0 55.3
						H: 3.52 4.38
5d	6-Br	H	40	242–243	$C_{17}H_{13}BrN_2O_3S$ (405.2)	6.9 6.8
5e	6,8-diBr	H	40	193	$C_{17}H_{12}Br_2N_2O_3S$ (484.1)	5.8 5.9

* The jelly like mass obtained from the reaction mixture was taken in dry ether and HCl gas was passed into it. The hydrochloride salt thus obtained was recrystallised from methanol. I. R. (KBr): **5a:** 1680 cm^{-1} (C=O).

Table 2: *3-[2-Styryl-4-(3H)-quinazolyl]phenyl-4'-mercaptoacetic acids* **6**

Compound No.	R	R'

Compound No.	R	R'	R''	Yield %	M.P. °C	Molecular formula (Mol.wt.)	Calcd. Found N
6a	H	H	H	60	218–219	$C_{24}H_{18}N_2O_3S$ (414.4)	6.8 7.0
6b	H	H	2–OH	60	> 272	$C_{24}H_{18}N_2O_4S$ (430.4)	6.5 5.9
6c	7-NO_2	H	2–OH	40	245–246	$C_{24}H_{17}N_3O_6S$ (475.4)	C: 60.6 60.6
							H: 3.60 3.50
6d	6-Br	H	2–OH	40	252–254	$C_{24}H_{17}BrN_2O_4S$ (509.3)	5.5 5.6

I. R. (KBr): **6d:** 1710 (C=O, carboxylic), 1650 cm^{-1} (C=O, ring).

Table 3: *3-[2-Phenyl-4-(3H)-quinazolyl]-phenyl-4'-mercaptoacetic acids* **8**

Compound No.	R	R'	Yield %	M.P. °C	Molecular formula (Mol.wt.)	Calcd. Found N
8a	H	H	50	165	$C_{22}H_{16}N_2O_3S$ (388.4)	7.2 8.0
8b	H	Me	50	172–173	$C_{23}H_{18}N_2O_3S$ (402.4)	7.0 7.3
8c	7-NO_2	H	60	210	$C_{22}H_{15}N_3O_5S$ (433.4)	C: 61.0 60.7 H: 3.48 4.00
8d	6-Br	H	60	220–221	$C_{22}H_{15}BrN_2O_3S$ (467.3)	6.0 6.3

I. R. (KBr): **8a:** 3000 (OH, carboxylic), 1680 (C=O, carboxylic), 1640 (C=O, ring), 1610 cm^{-1} (aryl).

Pharmacology

C. N. S. Activity (Table 4)

Eight compounds were tested for their C. N. S. activity in albino mice of either sex. The ALD_{50} were also determined[12]. For the C. N. S. screening the compounds were administered intraperitoneally (dose 464 mg/kg of the mice) as gum-accacia suspension and the gross behavioural changes were recorded.

Antibacterial Activity (Table 5)

All the compounds were screened for their antibacterial activity against B. subtilis and S. aureus by agar diffusion technique[13]. Four compounds (**3b, 5e, 6a** and **8d**) showed good inhibition against B. subtilis while only three compounds (**3b, 5a** and **6a**) were successful in inhibiting S. aureus. **3b** and **6a** being effective against both the organisms may be regarded as most active compounds. All the compounds were less effective in comparison to tetracycline which was taken as standard.

Antiviral Activity (Table 6)

In Vitro: – 1 ml of the solution (5 mg/ml) of the compound and 1 ml of the virus (T. M. V.) were mixed at room temp. and applied on the leaves of Chenopodium amaranticolor. Controls consisted of leaves rubbed with water mixed with virus in equal amounts.

In Vivo: The appropriate compound 2.5 mg/ml was applied on the 4 leaves of C. amaranticolor, 24 h before virus (1/100) inoculation. In controls distilled water was applied instead of the solution of the compounds. Local lesions were counted 4–6 d after virus inoculation. Percent inhibition was calculated by the formula

$$\frac{C - T}{C} \times 100$$

where C is the number of local lesions on control leaves and T on treated leaves. As is evident from the table 6 all the compounds have shown significant antiviral activity. The compounds are effective in controlling the virus in vitro as well as in vivo.

Table 4: *C. N. S. Activity*

Compound No.	ALD_{50}	SMA	React.	Resp.	Hypothermia	Other effects
3a	1000	↑	↑	↑	–	straub tail
5a	825	↓	↓	–	–	writhing
5b	562	↓	↓	–	–	writhing
5d	618	↑	↓	–	+ 0.3°	anoxia, ataxia, writhing
8a	383	↑	↑	–	–	–
8b	316	–	↑	↓ ↑	–	ataxia, anoxia, exophthalmus, writhing
8c	316	↓	↓	–	+ 0.5°	writhing
8d	316	↑	↓	↑ ↓	+ 0.5°	ataxia, anoxia, exophthalmus

ALD_{50} = Approximate lethal doses in 50 % of animals tested
SMA = Spontaneous motor activity
React. = Reactivity; Resp. = Rate of respiration; ↑ = Increased; ↓ = decreased; – = No effect; + = Present.

Table 5: *Antibacterial Activity*

Compound No.	*B. subtilis*	*S. aureus*
3a	–	–
3b	+++	+++
5a	–	+++
5b	–	–
5c	++	–
5d	–	–
5e	+++	–
6a	+++	+++
6b	–	–
6c	–	–
6d	–	–
8a	–	–
8b	++	–
8c	–	–
8d	+++	–

The experiments were carried out in duplicate.
– = no inhibition; + = inhibition, zone size 6–8 mm; ++ = inhibition, zone size 8–10 mm; +++ = inhibition, zone size greater than 10 mm.

Table 6: *Antiviral Activity*

Compound No.	% Inhibition	
	In Vitro	In Vivo
3a	63	83
3b	92	96
5a	82	89
5b	59	75
5d	73	92
5e	56	84
8a	71	55
8b	61	68

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