HYDROACRIDINES AND RELATED COMPOUNDS.

21.* SYNTHESIS OF 2-(2-THIENYL)HYDROQUINOLINES AND 2,7-DITHIAHYDROACRIDINES

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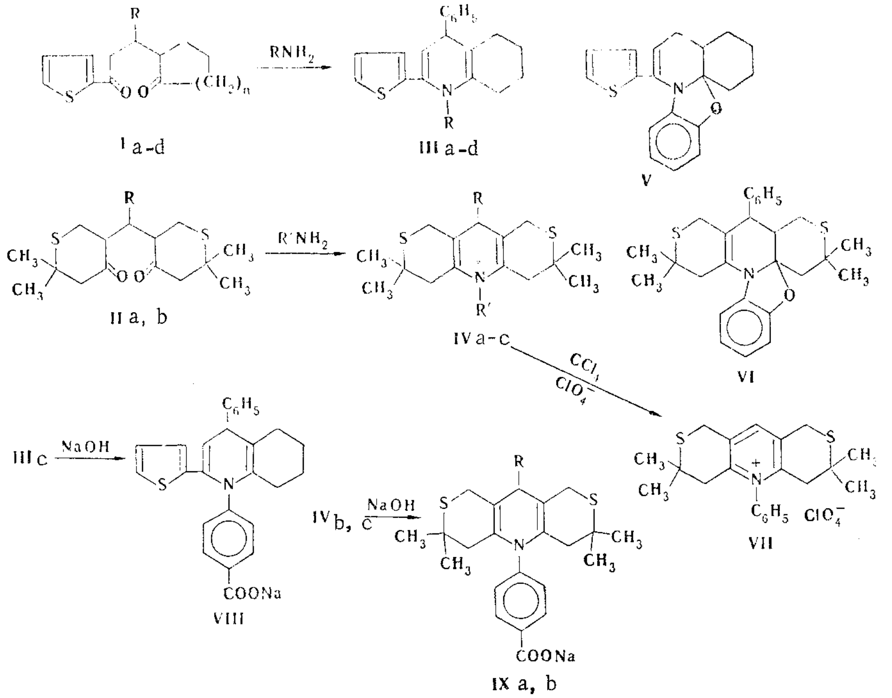
A number of sulfur-containing 1,5-diketones were synthesized and subjected to reaction with primary amines to give derivatives of 2-(α-thienyl)hydroquinolines and 2,7-dithiahydroacridines that contain 1,4-dihydropyridine and benzoxazolinotetrahydropyridine structures. The oxidation of some of the dihydropyridine derivatives was studied.

Continuing our research on the reaction of 1,5-diketones with primary amines [1] we studied the reaction of sulfur-containing 1,5-diketones Ia-d and IIa, b with primary amines in order to obtain compounds that have antioxidant activity. Diketone Ic was obtained in [2], whereas we synthesized the remaining ketones for the first time: Ia, b were synthesized by heating the Mannich base of α-acetothienone with the corresponding cyclanone at 140-150°C, Id was synthesized by the addition of cyclohexanone to p-hydroxybenzalacetothienone, and IIa, b were synthesized by diketone condensation of 2,2-dimethyltetrahydro-4-thiopyrone with the corresponding aldehydes.



I a $R=H$, $n=1$; b $R=H$, $n=2$; c $R=C_6H_5$, $n=2$; d $R=C_6H_4OH\text{-}4$, $n=2$; II, IX a $R=H$; b $R=C_6H_5$; III a $R=C_6H_5$; b $R=CH_2C_6H_5$; c $R=C_6H_4COOCH_3\text{-}4$; d R=α-naphthyl
IV a $R=C_6H_5$, $R'=CH_2C_6H_5$; b $R=H$, $R'=C_6H_4COOCH_3\text{-}4$; c $R=C_6H_5$, $R'=C_6H_4COOCH_3\text{-}4$

The reaction of the indicated diketones with primary amines yielded 1,4-dihydropyridine derivatives IIIa-d and IVa-c, while the reaction of diketones Ib and IIb with o-aminophenol

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*See [1] for Communication 20.

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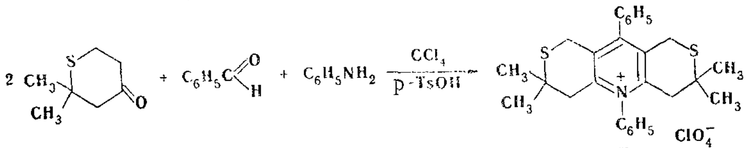
leads to, respectively, V and VI with a benzoxazolinotetrahydropyridine structure, as in the case of other 1,5-diketones [3]. Complex mixtures of products with high percentages of the starting diketones are formed in a number of cases (diketones Ia and Id) during attempts to carry out the reaction with primary amines; we were unable to isolate reaction products.

The IR spectra of IIIa-d contain two C=C absorption bands, one at 1630-1640 cm^{-1}, and the other at 1680 cm^{-1}. The C=C absorption in the spectra of Va-c also has the form of a doublet with one band at 1660-1670 cm^{-1} and the other at 1690-1700 cm^{-1}. The spectra of IIIc and IVb also contain absorption at 1720 cm^{-1} ($COOCH_3$). The spectra of V and VI do not contain OH absorption, and the region of C=C absorption contains a single band at 1640 cm^{-1} in the case of V and at 1670 cm^{-1} in the case of VI. The position of the C=C absorption band in the spectrum of V indicates the formation of an azoline ring on the side of the alicyclic fragment of diketone Ib.

The 1,4-dihydropyridine derivatives obtained proved to be more resistant to oxidation than the previously investigated decahydroacridines. Thus diketone IIa reacts with aniline and CCl_4 [4] to give pyridinium salt VII in relatively low yield, while p-aminobenzoic acid virtually does not undergo reaction under these conditions. Compound IVb decolorizes methylene blue almost an order of magnitude more slowly than 10-(p-carbomethoxyphenyl)decahydroacridine. Water-soluble carboxylate VIII reduces acridine to acridan under mild conditions; however, it does not reduce benzalacetophenone and benzalaniline, which are readily reduced by the analogous carboxylate of the decahydroacridine series [1].

We have demonstrated the possibility of the one-step synthesis of thia analogs of sym-octahydroacridinium salts in the case of the reaction of 2,2-dimethyltetrahydrothiopyrone, benzaldehyde, and aniline in the presence of CCl_4 and p-toluenesulfonic acid, as in the synthesis of sym-octahydroacridinium salts [5]. The corresponding salt (IX) was obtained in 40% yield.



X

EXPERIMENTAL

The IR spectra of mineral oil suspensions and solutions of the compounds in chloroform were recorded with a UR-20 spectrometer. The course of the reactions and the purity of the compounds obtained were monitored by thin-layer chromatography (TLC) on Silufol and activity II Al_2O_3. The characteristics of the synthesized compounds are presented in Table 1.

1-(α-Thienyl)-3-(2-oxocycloalkyl)propan-1-ones (Ia, b). 2-(3-Dimethylamino-1-propanonyl)thiophene was refluxed with a twofold molar excess of the corresponding cyclanone until dimethylamine liberation ceased (50 h in the case of Ia, as compared with 2 h in the case of Ib), after which the excess cyclanone was removed by distillation at reduced pressure. In the case of Ia the residue was distilled *in vacuo* with collection of the fraction with bp 172-176°C (6 mm) in the form of a viscous oil, which gradually began to crystallize. In the case of Ib the residue was passed through activity II Al_2O_3, and diketone Ib was eluted with diethyl ether; the residue after removal of the ether from the eluate by distillation was crystallized.

1-(α-Thienyl)-3-(p-hydroxyphenyl)-3-(2-oxocyclohexyl)propan-1-one (Id). An equimolar (with respect to the chalcone) amount of NaOH in the form of a 40% aqueous solution was added with stirring to a solution of p-hydroxybenzylidene-α-acetothienone and a threefold molar excess of p-hydroxybenzylidene-α-acetothienone and a threefold molar excess of cyclohexanone in ethanol (20 ml per gram of chalcone). After 24 h, the mixture was acidified with HCl (1:1) and diluted with a twofold volume of water. The liberated oil crystallized immediately, and Id was removed by filtration, washed with aqueous ethanol and water, and dried.

5,5'-Methylenebis(2,2-dimethyltetrahydro-4-thiopyrone) (IIa) and 5,5'-Benzylidenebis-(2,2-dimethyltetrahydro-4-thiopyrone) (IIb). An equimolar amount of a 2 N alcohol solution of NaOH was added with stirring to a heated (to 80°C) sample of 2,2-dimethyltetrahydro-4-thiopyrone, after which a 35% aqueous solution of formaldehyde or an alcohol solution of

TABLE 1. Properties of the Synthesized Compounds

Compound	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
Ia	49—50[a]	64,1	6,2	—	$C_{12}H_{14}O_2S$	64,5	6,3	—	35
Ib	50—51[a]	65,7	6,6	—	$C_{13}H_{16}O_2S$	66,1	6,8	—	53
Ic	135—136	72,5	6,5	—	$C_{19}H_{20}O_2S$	73,1	6,4	—	97
Id	177—178	69,8	6,3	—	$C_{19}H_{20}O_3S$	69,5	6,1	—	94
IIa	134—135	59,5	7,9	—	$C_{15}H_{24}O_2S_2$	60,0	8,0	—	95
IIb	166—167	66,3	7,2	—	$C_{21}H_{28}O_2S_2$	67,0	7,4	—	45
IIIa	98—99	81,0	6,2	3,8	$C_{25}H_{23}NS$	81,3	6,2	3,8	75
IIIb	79—80	81,2	6,4	3,8	$C_{26}H_{25}NS$	81,5	6,5	3,7	46
IIIc	116—117	75,2	6,0	3,0	$C_{27}H_{25}NO_2S$	75,9	5,9	3,3	66
IIId	104—105	83,1	5,9	3,4	$C_{29}H_{25}NS$	83,1	6,0	3,3	50
IVa	145—147	74,8	7,2	3,2	$C_{28}H_{33}NS_2$	75,2	7,4	3,1	56
IVb	144—146	66.1	6,5 (6,54)	3,5	$C_{23}H_{29}NO_2S_2$	66,5	7,0 (6,98)	3,4	66
IVc	>220[b]	70,8	6,8	3,0	$C_{29}H_{33}NO_2S_2$	70,3	6,7	2,9	69
V	135—136	73,2	6,3	4,3	$C_{19}H_{19}NOS$	73,8	6,1	4,5	65
VI	177—178	72,6	6,9	3,2	$C_{27}H_{31}NOS_2$	72,2	6,9	3,1	67
VII	232—234[b]	55,8	6,0	3,1	$C_{21}H_{26}NO_4S_2Cl$	55,3	5,7	3,1	39
VIII	>230[b]	—	—	2,8	$C_{26}H_{22}NO_2SNa$	—	—	3,0	60
IXa	>240[b]	—	—	3,4	$C_{22}H_{26}NO_2S_2Na$	—	—	3,3	72
IXb	260—263[b]	—	—	2,5	$C_{28}H_{30}NO_2S_2Na$	—	—	2,8	87
X	255—257	61,6	5,8	2,4	$C_{27}H_{30}NO_4S_2Cl$	61,0	5,6	2,6	40

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[a] From petroleum ether. The remaining compounds, with the exception of VIII and IXa, b, were recrystallized from ethanol. [b] With decomposition.

benzaldehyde (0.25 mole of the aldehyde per mole of ketone) was added dropwise, and the mixture was stirred for another 2 h. In the case of IIa the mixture was acidified to pH 4 with CH_3COOH, and diketone IIa was removed by filtration. An additional amount of diketone IIa precipitated after treatment of the filtrate with a solution of KOH in methanol. In the case of IIb the diketone precipitated immediately after cooling of the reaction mixture.

Reaction of Diketones Ia-d and IIa, b with Primary Amines. A) A solution of 2 g of the diketone, a 10% molar excess of the amine, and 20 mg of p-toluenesulfonic acid in 30 ml of xylene was refluxed with a Dean—Stark trap for 2-8 h, after which the xylene was evaporated at reduced pressure, the residue was treated with ethanol, and IIIa-d, IVa-c, V, and VI were removed by filtration.

B) A 1-g sample of diketone IIa and a 20% molar excess of the amine were refluxed in a solution of 20 ml of benzene and 3 ml of CCl_4, after which the mixture was extracted with water (three 10-ml portions), and the aqueous solution was extracted with ether (five 10-ml portions). A saturated solution of NH_4ClO_4 was added to the clear aqueous layer, and, in the case of aniline, precipitated perchlorate VII was removed by filtration, washed with water, and dried; in the case of p-aminobenzoic acid only traces of the perchlorate were formed.

Hydrolysis of IIIc and IVb, c. A solution of strictly equimolar amounts of the corresponding dihydropyridine and NaOH in absolute ethanol was refluxed for 1-2 h, after which the precipitated VIII and IXa, b were removed by filtration and washed with absolute ethanol, acetone, and ether. The carboxylates obtained were quite soluble in water.

Reduction of Acridine with VIII. A 0.3-g sample of carboxylate VIII was dissolved in 10 ml of 70% ethanol, 60 mg of acridine was added, and the mixture was allowed to stand at 20°C. After 2 h, the mixture was diluted with 20 ml of water, and 50 mg of acridan was removed by filtration. The product was identical to a genuine sample. Benzylideneacetophenone was not converted to benzalaniline under the same conditions.

3,3,6,6-Tetramethyl-9,10-diphenyl-2,7-dithia-sym-octahydroacridinium Perchlorate (X). A mixture of 0.055 mole of 2,2-dimethyltetrahydro-4-thiopyrone, 0.027 mole of benzaldehyde, 0.027 mole of aniline, 8 ml of CH_3COOH, 10 ml of CCl_4, 50 ml of xylene, and 50 mg of p-toluenesulfonic acid was refluxed with a water separator for 2 h, after which it was extracted with water (four 10-ml portions), and the aqueous extract was extracted with ether. A saturated solution of NH_4ClO_4 was added to the clear aqueous layer, and perchlorate X was removed by filtration, washed with water, and dried.

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RESEARCH ON UNSATURATED LACTONES.

49.* SYNTHESIS OF THIAZOLIDINES THAT CONTAIN AN α,β-UNSATURATED γ-LACTONE RING

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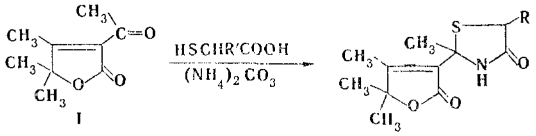
The corresponding thiazolidines containing a lactone ring and their hydrochlorides and N-benzoyl derivatives were obtained by the reaction of 2-acetyl-3,4,4-trimethyl-2-buten-4-olide with thioglycolic or mercaptosuccinic acids and ammonium carbonate.

It is known that many thiazolidine derivatives are biologically active substances; in particular, they have analgesic, antipyretic, and antibacterial activity [2, 3].

In order to synthesize new biologically active thiazolidine derivatives that contain an α,β-unsaturated γ-lactone ring we studied the reactions of 2-acetyl-3,4,4-trimethyl-2-buten-4-olide (I) with thioglycolic and mercaptosuccinic acids and ammonium carbonate.

2-Methyl-2-(3,4,4-trimethyl-2-buten-4-olid-2-yl)-4-oxothiazolidine (II) is formed in 20-32% yield from thioglycolic acid. The reaction with mercaptosuccinic acid proceeds more readily and gives a decarboxylated product, viz., 2,5-dimethyl-2-(3,4,4-trimethyl-2-buten-4-olid-2-yl)-4-oxothiazolidine (III), in 40% yield. Refluxing in xylene leads to considerable resinfication.



I

$R'=H,\ CH_2COOH$

II $R=H$; III $R=CH_3$

Absorption bands that are characteristic for lactone (1745-1750 cm^{-1}) and lactam (1695-1700 cm^{-1}) carbonyl groups, a double bond (1590-1620 cm^{-1}), and an NH group (3180-3200 cm^{-1}) are found in the IR spectra of the compounds obtained. The PMR spectrum of III contains, in addition to signals of protons of methyl groups in the 3 and 4 positions of the butenolide ring (2.08 and 1.53 ppm) and in the 2 position of the thiazolidine ring (1.18 ppm), of an NH group (13.09 ppm), and a proton in the 5 position of the thiazolidine ring (4.48 ppm), a signal of protons of a methyl group in the same position (2.18 ppm).

Hydrochlorides IV and V are formed from thiazolidines II and III in 30-40% yields. Reverse alkalization again gives the free thiazolidines.

Reactions with benzoyl chloride lead to the formation of N-benzoyl derivatives VI and VII in 45-50% yields. The IR spectra of VI and VII contain absorption bands at 1750-1755,

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*See [1] for Communication 48.

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