123. Structural Analogues of Aporphines
Part 1: Synthesis of Apomorphines with the Catechol Moiety Replaced by 5-membered Heterocycles

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Summary

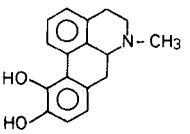
Analogues of apomorphine (**1**) having the catechol moiety replaced by pyrrole (→ **10**, **18**), pyrazole (→ **12**), isoxazole (→ **13**, **14**), thiazole (→ **16**) and thiadiazole (→ **20**) ring systems have been synthesized from the key intermediate ketone **6**.

Introduction. – In connection with studies of modified aporphines it was of interest to synthesize analogues of apomorphine (**1**) where the catechol moiety, which is important for biological activities, is replaced by 5-membered heterocycles such as pyrrole or pyrazole. For the synthesis of such structures the 1-methyl-2,3,7,8,9,9a-hexahydro-1*H*-benzo[*de*]quinolin-7-one (**6**) was required as a key intermediate. In the literature, only ketones substituted at the benzene ring by alkoxy or/and hydroxy groups in positions 5 and 6 have been reported [1]. In these syntheses, the activating effect of the alkoxy group in position 5 was necessary to promote the *Bischler-Napieralski* synthesis of their isoquinoline system. In the present work, a different approach had to be chosen for the construction of the unsubstituted key intermediate **6**.

The 5-membered heterocycles to be described in this paper were all built up from the ketone **6** by means of known methods.

Results. – The isoquinolinium iodide **2** was converted by 2N NaOH into the enamine **3** [2] which was then allowed to react with ethyl bromoacetate to give the 1-isoquinolinepropionate derivative **4**. The latter was reduced with $NaBH_4$ to **5** which was then cyclized in polyphosphoric acid (PPA) to the key intermediate **6**.

The pyrrolo compound **10** was prepared from ketone **6** by a modified *Knorr* synthesis. Reaction of **6** with ethyl formate in the presence of sodium ethoxide gave



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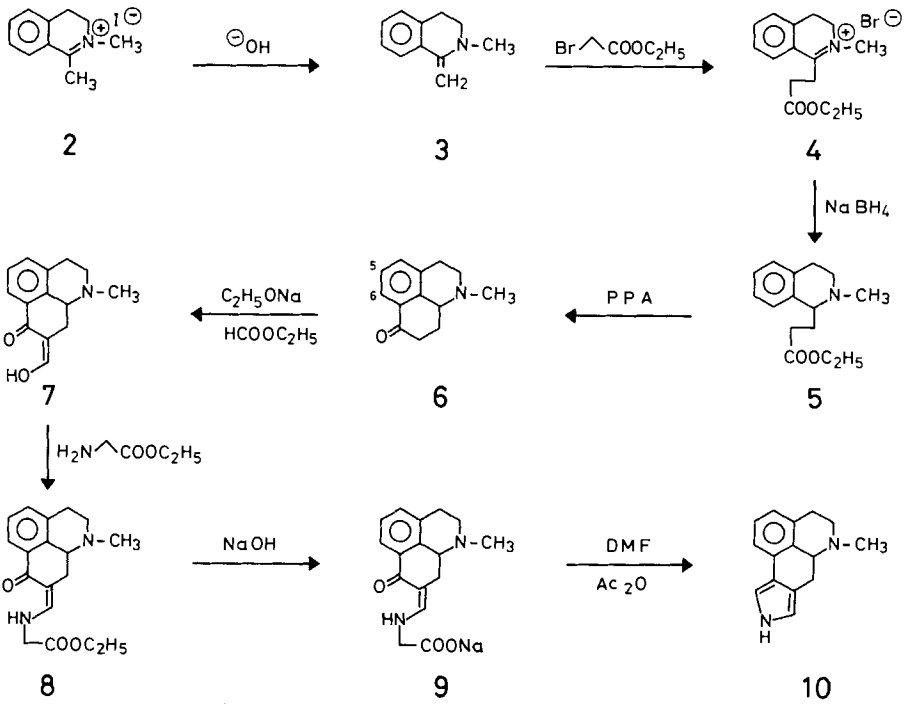


in good yield the hydroxymethylidene derivative **7** which, on condensation with glycine ethyl ester, was converted to **8**. The product of saponification **9** was cyclized and decarboxylated [3] on heating in DMF in the presence of acetic anhydride to yield the benzopyrroloquinoline **10**.

The pyrazolo analogue **12** was prepared by treating the hydroxymethylidene ketone **7** with semicarbazide and cyclizing the resulting product **11** by heating with 5 N H_2SO_4 [4].

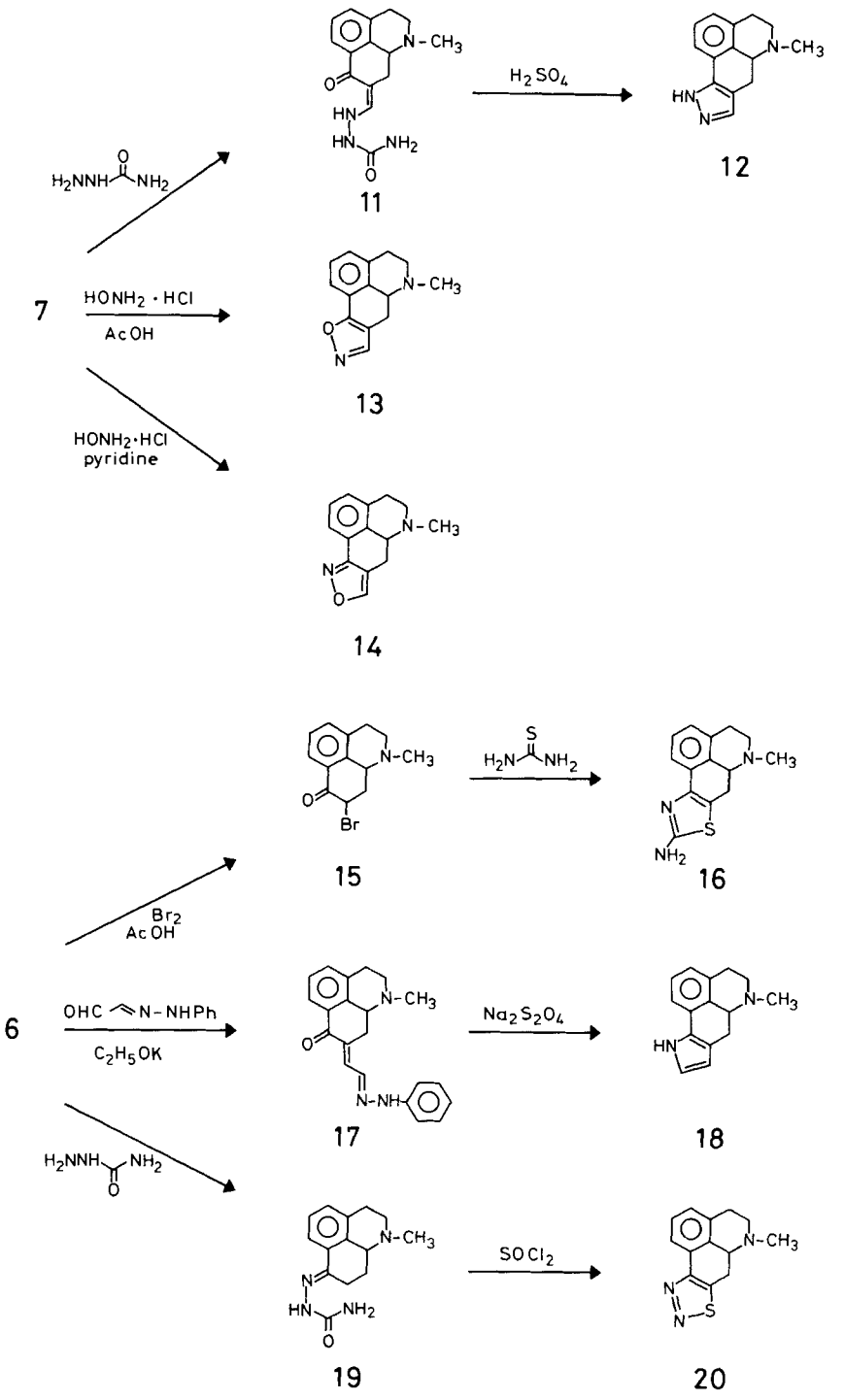
Also from compound **7** were obtained the isoxazolo compound **13** on treatment with hydroxylamine hydrochloride in acetic acid [4] [5], and the isomer **14** on treatment with hydroxylamine in pyridine [5].

The synthesis of the amino-thiazolo derivative **16** was effected by reacting ketone **6** with bromine in acetic acid and condensing the resulting bromo ketone **15** with thiourea [6].

Moreover, ketone **6** was reacted with glyoxal monophenylhydrazone in the presence of potassium ethoxide as condensing agent, and the resulting phenylhydrazone derivative **17** treated with sodium dithionate, to give the desired pyrroloquinoline **18** in rather low yields [7].

Finally, the thiadiazolo analogue **20** was prepared by treating the semicarbazone **19** with thionyl chloride [5].

Some of the compounds described, *e.g.* **10** and **12**, have shown dopaminergic activity like apomorphine.


7
6
$H_2NNH{-}C(=O){-}NH_2$
$HONH_2 \cdot HCl$
AcOH
$HONH_2 \cdot HCl$
pyridine
OHC–CH=N–NHPh
C_2H_5OK
$H_2NNH{-}C(=O){-}NH_2$
Br_2
AcOH
H_2SO_4
$H_2N{-}C(=S){-}NH_2$
$Na_2S_2O_4$
$SOCl_2$
N-CH3
NH2
Br
11
12
13
14
15
16
17
18
19
20

Experimental Part

General remarks. ^{1}H-NMR. spectra were taken at 60 MHz in $CDCl_3$ using a *Varian T-60* NMR. spectrometer. In case of salts, a sample of the free base was prepared and used in $CDCl_3$. Abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, *qa* = quadruplet, *qi* = quintuplet, *m* = multiplet, br. = broad; chemical shifts in relative to the internal standard tetramethylsilane (= 0 ppm); coupling constants *J* in Hz.

Synthesis of 1-[2-(ethoxycarbonyl)ethyl]-2-methyl-3,4-dihydroisoquinolinium bromide (**4**). The isoquinolinium iodide **2** (63 g, 0.22 mol) was dissolved in H_2O and the solution made alkaline with 2N NaOH. The solution was then extracted twice with toluene (100 ml). The extract, which contained the enamine **3**, was dried over Na_2SO_4 and filtered. To this solution under N_2, ethyl bromoacetate (43 g, 0.26 mol) in toluene (60 ml) was added at r.t., within 45 min and with stirring. The mixture was allowed to stand at r.t. for further 3 h. Then **4** was filtered off, washed with toluene and dried under vacuum: 69 g of crude **4**). A small amount was recrystallized from ethanol/ether for elemental analysis, m.p. 142–144°.

$C_{15}H_{20}BrNO_2$ (326.2) Calc. C 55.2 H 6.2 N 4.3% Found C 54.9 H 6.0 N 4.4%

Synthesis of ethyl 2-methyl-1,2,3,4-tetrahydro-1-isoquinolinepropionate (**5**). Crude **4** (69 g) was dissolved in ethanol (500 ml) and reduced at 0–5° with $NaBH_4$ (13 g, 0.034 mol). After working up, the product was distilled under reduced pressure; the second fraction collected between 100 and 120°/10–15 Torr consisted of pure **5** (24.9 g, 46% calculated from **2**). – ^{1}H-NMR.: 7.15 (*s*, 4 H arom.); 4.1 (*qa*, CH_3CH_2O); 2.45 (*s*, H_3C-N); 1.2 (*t*, CH_3CH_2O).

*Synthesis of 1-methyl-2,3,7,8,9,9a-hexahydro-1*H*-benzo*[de]*quinolin-7-one hydrochloride* (**6** · HCl). Compound **5** (180 g, 0.73 mol) was heated in PPA (3500 g) at 140° for 1 h, with stirring. After cooling to about 60°, the mixture was poured into ice/water, made alkaline with 30% NaOH-solution and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried and evaporated to dryness. The compound was allowed to crystallize from ethanol/ether as **6** · HCl (55.4 g, 32%), m.p. > 300°, free base **6** m.p. 61–64°. – ^{1}H-NMR.: 7.9 (*m*, H–C(6)); 2.5 (*s*, H_3C-N).

$C_{13}H_{16}ClNO$ (237.7) Calc. C 65.7 H 6.8 N 5.9% Found C 65.6 H 6.8 N 6.0%

*Synthesis of 8-hydroxymethylidene-1-methyl-2,3,7,8,9,9a-hexahydro-1*H*-benzo[*de*]quinolin-7-one* (**7**). Abs. ethanol (9.2 g, 0.2 mol) was mixed with benzene (250 ml), and a 50% NaH dispersion in mineral oil (9.6 g, 0.2 mol) was added with stirring under N_2. Ethyl formate (14.8 g, 0.2 mol) was added, followed by **6** (20.1 g base, 0.1 mol), and the mixture was kept for 24 h at r.t. Then the mixture was extracted with H_2O (3 times 30 ml), the aqueous extract containing the sodium salt of **7** made slightly acid, then buffered with 2N $KHCO_3$ and extracted with CH_2Cl_2. The organic extract was dried and evaporated. The residue was recrystallized from ethanol at –20° giving 17.7 g (77%) of **7**, m.p. 129–131°. – ^{1}H-NMR.: 8.35 (*s*, H olef.); 7.75 (*m*, H–C(6)); 2.5 (*s*, H_3C-N).

$C_{14}H_{15}NO_2$ (229.3) Calc. C 73.3 H 6.6 N 6.1% Found C 73.4 H 6.7 N 6.0%

Synthesis of N*-[(1-methyl-7-oxo-2,3,7,8,9,9a-hexahydro-1*H*-benzo[*de*]quinolin-8-yliden)methyl]-glycine ethyl ester monohydrochloride* (**8** · *HCl*). Compound **7** (13.8 g, 0.06 mol) was dissolved in warm methanol (200 ml), and glycine ethyl ester hydrochloride (12.6 g, 0.09 mol) in methanol (90 mol) was added with stirring. The product was filtered and recrystallized from methanol at –20°, giving 17.6 g (84%) of **8** · HCl, m.p. 215° (dec.). – ^{1}H-NMR.: 10.2 (br. *qi*, HN, disappears after D_2O exchange); 7.8 (*m*, H–C(6)); 6.8 (*d*, *J* = 12, H olef., collapses to *s* after D_2O exchange); 4.2 (*qa*, CH_3CH_2O); 4.0 (*d*, *J* = 6, CH_2COOEt, collapses to *s* after D_2O exchange); 2.4 (*s*, H_3C-N); 1.25 (*t*, CH_3CH_2O).

$C_{18}H_{23}ClN_2O_3$ (350.9) Calc. C 61.6 H 6.6 N 8.0% Found C 61.7 H 6.5 N 8.1%

Synthesis of N*-[(1-methyl-7-oxo-2,3,7,9,9a-hexahydro-1*H*-benzo[*de*]quinolin-8-ylidene)methyl]-glycine sodium salt* (**9**). Compound **8** (16.2 g base, 0.0515 mol) was dissolved in abs. ethanol (180 ml), and NaOH-pellets (13 g, 0.325 mol) were added. The mixture was heated to 50° for 45 min and then cooled in ice/water for 1 h. The solid was filtered off, washed with cold ethanol and dried giving 14.4 g (91%) of **9**, m.p. 250° (dec.).

$C_{16}H_{17}NaN_2O_3$ (308.3) crude **9** Calc. C 62.3 H 5.6 N 9.1% Found C 60.5 H 5.6 N 8.9%

*Synthesis of 6-methyl-4,5,6,6a,7,9-hexahydrobenzo[*de*]pyrrolo[3,4-*g*]quinoline* (**10**). Salt **9** (19.7 g, 0.064 mol) was suspensed in a mixture of DMF (160 ml), acetic anhydride (24.1 ml, 0.22 mol) and sodium acetate (31.7 g, 0.38 mol). The mixture was heated at 100° under N_2 with stirring for 1.5 h. Ice cold water (700 ml) and aq. 30% NaOH-solution (92 g) were added, and the solid which separated was filtered off and recrystallized from cold ethanol to give 4.8 g (33%) of **10**, m.p. 204–207°. – ^{1}H-NMR.: 8.5 (br. *m*, HN); 6.9 and 6.5 (2 narrow *m*, H–C(8) and H–C(10), collapse to narrower signals after D_2O exchange); 2.55 (*t*, CH_3N).

$C_{15}H_{16}N_2$ (224.3) Calc. C 80.3 H 7.2 N 12.5% Found C 80.3 H 7.0 N 12.6%

*Synthesis of 6-methyl-4,5,6,6a,7,10-hexahydrobenzo[*de*]pyrazolo[3,4-*g*]quinoline* (**12**). Compound 7 (15.95 g, 0.0695 mol) was dissolved in ethanol (150 mol), and a solution of semicarbazide hydrochloride (7.75 g, 0.0695 mol) and sodium acetate (5.7 g, 0.0695 mol) in water (50 ml) was added dropwise. The mixture was cooled in ice/water for 1 h and the crude product **11** filtered off, dried and heated under reflux in H_2SO_4/H_2O 1:3 for 15 min. The mixture was made alkaline, extracted with CH_2Cl_2 and the extract evaporated. The residue was recrystallized from CH_2Cl_2/ether, yielding 12.3 g (79%) of **12**, m.p. 194–196°. – ^{1}H-NMR.: 12 (very br., HN); 7.4 (*s*, H–C(8)); 2.55 (*s*, H_3C–N).

$C_{14}H_{15}N_3$ (225.3) Calc. C 74.6 H 6.7 N 18.7% Found C 74.3 H 6.6 N 18.4%

*Synthesis of 6-methyl-5,6,6a,7-tetrahydro-4*H*-benzo[*de*]isoxazolo[5,4-*g*]quinoline hydrochloride* (**13** · *HCl*). To a solution of **7** (5 g, 0.022 mol) in acetic acid (80 ml), $NH_2OH \cdot HCl$ (2.4 g, 0.034 mol) was added, the mixture was heated for 1 h at 80°, then poured into ice/water (100 ml) and the solution made alkaline with 2N NaOH and extracted with CH_2Cl_2. The organic extract was dried and evaporated, and the residue treated with ethanol and HCl/ether to give 4.8 g (83%) of **13** · HCl, m.p. >300°. – ^{1}H-NMR.: 8.2 (*s*, H–C(8)); 7.45 (*d*×*d*, H–C(1)); 2.5 (*s*, CH_3N).

$C_{14}H_{15}ClN_2O$ (262.7) Calc. C 63.8 H 6.1 N 10.6% Found C 63.5 H 5.7 N 10.8%

*Synthesis of 6-methyl-5,6,6a,7-tetrahydro-4*H*-benz[*de*]isoxazolo[3,4-*g*]quinoline* (**14**). Compound 7 (6.67 g, 0.03 mol) was dissolved in pyridine (75 ml), and a solution of $NH_2OH \cdot HCl$ (5.01 g, 0.072 mol) in water (9.6 ml) was added dropwise. The mixture was then heated under reflux for 6 h, cooled and diluted with water (600 ml). The product was extracted with CH_2Cl_2, recrystallized from ether and recrystallized from ethyl acetate, giving 4.2 g (62 %) of **14**, m.p. 96–98°. – ^{1}H-NMR.: 8.2 (finely split *s*, H–C(8)); 7.8 (*d*×*d*, H–C(1)); 2.5 (*s*, H_3C–N).

$C_{14}H_{14}N_2O$ (226.3) Calc. C 74.3 H 6.2 N 12.4% Found C 74.3 H 6.1 N 12.6%

*Synthesis of 8-bromo-1-methyl-2,3,7,8,9,9a-hexahydro-1*H*-benzo[*de*]quinolin-7-one hydrobromide* (**15** · *HBr*). To a solution of **6** (20 g, 0.099 mol) in acetic acid (300 ml), 30% HBr in acetic acid (23 ml, ~0.12 mol) was added at r.t., followed by bromine (16.4 g, 0.11 mol) which was added dropwise within 1 h, with stirring. During the first 5 min of the bromine addition, the mixture was illuminated with a 500 W tungsten lamp. Then it was allowed to stand at r.t. before the product was filtered off, washed with acetic acid, ether and dried, giving 31.4 g (88%) of crude **15** · HBr, m.p. >260°. – ^{1}H-NMR.: 8.0 (*m*, H–C(6)); 4.8 (*t*, *J* = 3, H–C(8)); 2.5 (*s*, H_3C–N).

*Synthesis of 6-methyl-5,6,6a,7-tetrahydro-4*H*-benzo[*de*]thiazolo[4,5-*g*]quinoline-9-amine dihydrobromide* (**16** · *2 HBr*). Thiourea (2.93 g, 0.0385 mol) was added to a suspension of **15** · HCl (12.6 g, 0.035 mol) in abs. ethanol (500 ml). The mixture was refluxed for 2 h and then cooled to allow the product to crystallize. Recrystallization from H_2O/DMF/ether gave 9.5 g (65%) of **16** · 2 HBr, m.p. 250° (dec.). Also **16** · 2 HCl was prepared, m.p. 200° (dec.). – ^{1}H-NMR.: 5.3 (br. *s*, H_2N); 2.5 (*s*, CH_3N).

$C_{14}H_{17}Cl_2N_3S$ (330.3) Calc. C 50.9 H 5.2 N 12.7% Found C 50.8 H 5.0 N 12.6%

*Synthesis of (1-methyl-7-oxo-2,3,7,8,9,9a-hexahydro-1*H*-benzo[*de*]quinolin-8-yliden)acetaldehyde phenylhydrazone* (**17**). Potassium (2 g, 0.051 mol) was added portionwise under N_2 to abs. ethanol (25 ml). To the EtOK-solution (2.01 g, 0.01 mol), glyoxal monophenylhydrazone (1.48 g, 0.01 mol) dissolved in abs. ethanol (20 ml) was added at r.t. After further 15 min at r.t., the mixture was evaporated to dryness at 30° and the residue treated with 0.33N CH_3COOH (155 ml, 0.051 mol). The mixture was then

extracted with CH_2Cl_2 and the dried extract evaporated to dryness. The residue was crystallized from CH_2Cl_2/ether, giving 1.6 g (48%) of crude **17**, m.p. 176–178° (dec.).

*Synthesis of 6-methyl-4,5,6,6a,7,10-hexahydro-benzo[*de*]pyrrolo[2,3-g]quinoline* (**18**). To a suspension of **17** (17 g, 0.051 mol) in ethanol/H_2O 2:1 (15 ml), $Na_2S_2O_6$ (70.9 g, 0.407 mol) was added with stirring and the mixture was heated under reflux for 3 h. Then water (1360 ml) was added, the mixture extracted with CH_2Cl_2, and the extract dried and evaporated. The residue was dissolved in toluene, treated with charcoal, filtered and cooled to −20°, giving 3.05 g (27%) of **18**, m.p. 157–159°. – ^{1}H-NMR.: 8.8 (br., HN); 6.5 and 6.05 (2 narrow *t*, H–C(8) and H–C(9), collapse to *d* after D_2O exchange); 2.5 (*s*, H_3C–N).

$C_{15}H_{16}N_2$ (224.3) Calc. C 80.3 H 7.2 N 12.5% Found C 80.1 H 7.5 N 12.4%

*Synthesis of 1-(1-methyl-2,3,7,8,9,9a-hexahydro-1*H*-benzo[*de*]quinolin-7-ylidene)semicarbazide hydrochloride (***19*** · HCl).* A suspension of **6** (8.04 g, 0.04 mol) and semicarbazide hydrochloride (5.4 g, 0.048 mol) in methanol (200 ml) was heated under reflux for 15 min. After cooling, the solid was filtered off, washed with cold methanol and dried under vacuum to give 11.3 g (96%) of crude **19** · HCl, m.p. 220–300° (dec.).

$C_{14}H_{19}ClN_4O$ (294.8) crude **19** · HCl Calc. C 57.0 H 6.5 N 19.0% Found C 56.0 H 6.6 N 18.7%

*Synthesis of 6-methyl-5,6,6a,7-tetrahydro-4*H*-benzo[*de*][1,2,3]thiadiazolo[4,5-g]quinoline* (**20**). Within 15 min **19** · HCl (12 g, 0.04 mol) was added in small portions to $SOCl_2$ (144 ml) at 0–5°. The mixture was allowed to stand for further 15 h at r.t. Then CH_2Cl_2 (400 ml) was added, the mixture poured with stirring into an ice cooled solution of Na_2CO_3 (1060 g in 4000 ml H_2O), the organic phase separated, dried and evaporated, and the residue recrystallized from ether, giving 7.5 g (77%) of **20**, m.p. 102–106°. – ^{1}H-NMR.: 8.1 (finely split *d*, H–C(1)); 7.25 (*t*, H–C(2)); 7.1 (finely split *d*, H–C(3)); 3.8 (*d*×*d*, *J* = 8 and 14, H–C(7)); 2.5 (*s*, H_3C–N).

$C_{13}H_{13}N_3S$ (243.3) Calc. C 64.2 H 5.4 N 17.3% Found C 64.2 H 5.3 N 17.4%

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