

**THIOXANTHENE DERIVATIVES WITH NEUROTROPIC ACTIVITY;
SYNTHESIS OF 9-(3-DIMETHYLAMINOPROPYLIDENE)-
-2-(METHYLTHIOMETHYL)THIOXANTHENE
AND OF SOME RELATED COMPOUNDS**



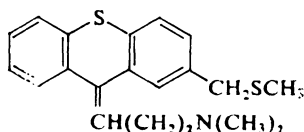
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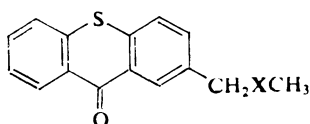
A reaction of 2-(bromomethyl)thioxanthone with sodium methanethiolate gave 2-(methylthiomethyl)thioxanthone (*II*) which was transformed by treatment with 3-dimethylaminopropylmagnesium chloride to the tertiary alcohol *IV*. Its dehydration by heating with dilute sulfuric acid afforded the title compound *I*. An attempt at preparing the analogous 2-(methoxymethyl) derivative proceeded similarly but failed in the stage of the acid-catalyzed dehydration of the tertiary alcohol *V*. Acids *VIII*–*XII* and the nitrile *XIII* were prepared as potential intermediates. Compound *I* has properties of a tranquilizer with a weak cataleptic activity.

Out of the alkyl groups, which are present in molecules of the tricyclic neuroleptics and fulfil the function of the „neuroleptic substituents” (ref.^{1,2}), methyl, ethyl and isopropyl proved most favourable, while n-propyl and n-butyl appear as less suitable which is probably the result of their already too emphasized hydrophobic character; our personal experience in this line relates to the 2-alkyl derivatives of 9-(3-dimethylaminopropylidene)thioxanthene (prothixene series)³ and to 8-alkyl derivatives of 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (perathiepin series)^{4–7}. Until present the effect of the methoxymethyl and methylthiomethyl groups as „neuroleptic substituents” has been unknown; they may be considered oxa and thia analogues of n-propyl with a hydrophobic character significantly suppressed by the presence of the oxygen or sulfur atom. The main object of the present study was the synthesis of 2-(methylthiomethyl) derivative of prothixene (*I*) and an attempt at preparing the analogous methoxymethyl compound.



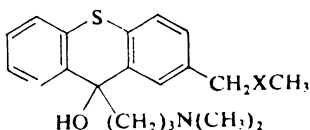
I

In the synthesis of compound *I* we first tried to proceed *via* 4-(methylthiomethyl)-thiophenol. The attempt failed already in the stage of reaction of benzyl methyl sulfide⁸ with chlorosulfonic acid in chloroform at room temperature: There resulted mostly water-soluble substances indicating cleavage of the benzyl-S bond. The instability of this bond, as well as of the similar benzyl-O bond, in acid media was the main difficulty we met during this work. We found then a useful intermediate in 2-(bromomethyl)thioxanthone⁹. A reaction of this compound with sodium methanethiolate in a mixture of methanol and acetone afforded the desired 2-(methylthiomethyl)thioxanthone (*II*) whose identity was corroborated by spectra. Treatment of the ketone *II* with 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran (analogy¹⁰) gave the tertiary alcohol *IV*. Its dehydration was carried out by heating with dilute sulfuric acid to 100°C. The crude base *I* was purified by chromatography on aluminium oxide and afforded a hydrogen oxalate. The mass spectrum of this compound confirmed for the base the expected elemental composition $C_{20}H_{23}NS_2$ (m/z 341). The pure base, which was released from the oxalate, was used for recording the 1H NMR and IR spectra (in carbon disulfide), which confirmed the structure *I*. In the IR spectrum there is an important band at 892 cm^{-1} which corresponds to the C—H bond of the solitary hydrogen atom in position 1 of the skeleton. With regard to the fact that the position of this band is just on the borderline between values typical for *Z*-isomers (910 cm^{-1}) and *E*-isomers (880 cm^{-1}) and the second geometrical isomer is not at disposal, the assignment of configuration on the double bond is hardly possible in this case³.



II, X = S

III, X = O

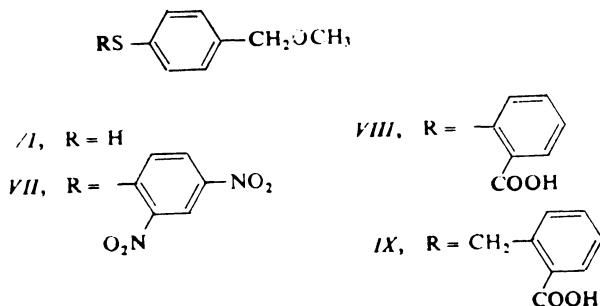


IV, X = S

V, X = O

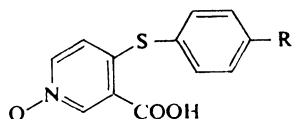
In an attempt at preparing the 2-(methoxymethyl) analogue of compound *I*, 4-(methoxymethyl)thiophenol (*VI*) was synthesized. 4-Bromobenzyl methyl ether¹¹ was transformed to the Grignard reagent in tetrahydrofuran and its treatment with sulfur gave *VI* in a yield of 68%. The same compound was prepared in a similar yield by a reaction of 4-bromobenzyl methyl ether¹¹ with excessive sodium methanethiolate in hexamethylphosphoric triamide at 100°C (analogy¹²). The oily *VI* was transformed for characterization to the S-(2,4-dinitrophenyl) derivative *VII* by treatment with 2,4-dinitrofluorobenzene in boiling methanol in the presence of 1M-NaOH. The sulfide *VII* enabled spectral identification of the thiol *VI*. Reaction of thiol *VI*

with 2-iodobenzoic acid in boiling aqueous potassium hydroxide solution in the presence of copper gave the acid *VIII*. Attempts to cyclize this acid to the ketone *III* with polyphosphoric or sulfuric acid were unsuccessful. A cleavage of the unstable benzyl-O bond takes place (this cleavage proceeds at room temperature already). Reaction of the sodium salt of the thiol *VI* with phthalide in boiling ethanol afforded the acid *IX*. The attempts to cyclize this acid to 2-(methoxymethyl)dibenzo[*b,e*]-thiepin-11(6*H*)-one by means of polyphosphoric acid in 1,2-dichloroethane at 80°C or with zinc chloride in a boiling mixture of acetic acid and acetic anhydride (analogy¹³) were unsuccessful again on the basis of the preferential cleavage of the benzyl-O bond. The ketone *III* was then prepared similarly like in the methylthiomethyl series, *i.e.* by reaction of 2-(bromomethyl)thioxanthone⁹ with a methanolic potassium hydroxide solution; its identity was fully confirmed by spectra. A similar attempt to prepare 2-(methoxymethyl)dibenzo[*b,e*]thiepin-11(6*H*)-one did not lead to the goal because the bromination of 2-methyldibenzo[*b,e*]thiepin-11(6*H*)-one¹³ with N-bromosuccinimide resulted in a mixture of compounds from which it did not succeed to isolate the desired 2-(bromomethyl) derivative. Reaction of the ketone *III* with 3-dimethylaminopropylmagnesium chloride in ether gave the tertiary alcohol *V*. The attempts at its dehydration were carried out by the use of hydrogen chloride in boiling acetic acid, with oxalic acid in boiling toluene, with boiling dilute sulfuric acid and with phosphoryl chloride in pyridine. There resulted complex mixtures from which it did not succeed to isolate crystalline products (neither in the form of salts); this negative result must be at least partly again ascribed to the cleavage of the benzyl-O bond.

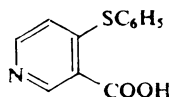


Finally, the preparation of three pyridine and one pyridazine derivatives as potential intermediates in the syntheses of sulfur-containing tricyclic skeletons is described. The synthesis of the acids *X* and *XI* used the ability of 4-nitronicotinic acid 1-oxide^{14,15} to displace the nitro group in reactions with nucleophiles without the simultaneous N-oxide reduction¹⁶. Reactions of the mentioned nitro acid N-oxide with thiophenol and 4-chlorothiophenol in dimethylformamide in the presence

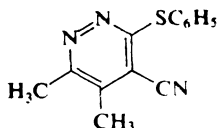
of potassium carbonate at 50–60°C gave the acids *X* and *XI*. Heating 4-chloro-nicotinic acid¹⁷ with a 100% excess of 4-chlorothiophenol in dimethylformamide to 140–145°C afforded the acid *XII* in a satisfactory yield. Finally, the known 3-chloro-5,6-dimethylpyridazine-4-carbonitrile¹⁸ reacted with thiophenol and potassium carbonate in dimethylformamide at 110°C and gave the nitrile *XIII*.



X, R = H
XI, R = Cl



XII



XIII

The title compound *I* was pharmacologically tested in the form of the hydrogen oxalate (ethanol solvate) on oral administration. The acute toxicity in mice, $LD_{50} = 400$ mg/kg. In the rotarod test in mice ataxia is brought about by doses of 10 to 80 mg/kg. The hypothermic effect in rats (reduction of the rectal temperature by 1°C) is shown already by doses of 1–10 mg/kg (in this test compound *I* is equipotent with chlorpromazine). Doses of 10–80 mg/kg prolong the thiopental sleeping time in mice to 200% of the control value (for chlorpromazine, $ED = 1$ mg/kg). Doses of 25–80 mg/kg inhibit significantly the spontaneous activity of mice. A dose of 80 mg/kg has a clear cataleptic activity in rats (weaker than chlorpromazine in a dose of 10 mg/kg). A dose of 80 mg/kg did show neither the antiamphetamine effect in mice nor the antiapomorphine effect in rats. Compound *I* is a mild tranquilizer with a significant hypothermic action and a weak cataleptic activity.

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler's block and they are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at 77°C or at room temperature. The UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (Nujol) with a Perkin Elmer 298 spectrophotometer, 1H NMR spectra (in C^2HCl_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectrum with a Varian MAT 44S spectrometer. The homogeneity of the compounds and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol).

2-(Methylthiomethyl)thioxanthone (II)

A solution of 16.2 g 2-(bromomethyl)thioxanthone⁹ in 100 ml acetone was added to a solution of 5.0 g sodium methanethiolate in 50 ml methanol and the mixture was refluxed for 2 h. Standing overnight at room temperature led to crystallization, the product was filtered, suspended in water, the suspension was stirred for 10 min and filtered; 11.0 g (75%), m.p. 107–11°C. Analytical sample, m.p. 110–112°C (ethanol). UV spectrum: $\lambda_{\max}$ 260 nm (log ϵ 4.66). 386 nm (3.75), inflexes at 291 nm (3.83) and 302 nm (3.69). IR spectrum: 740, 828, 868 (4 and 2 adjacent and solitary Ar—H), 1 590, 1 602, 3 010, 3 040, 3 058 (Ar), 1 632 cm^{-1} (ArCOAr'). ¹H NMR spectrum: δ 8.65 (m, 1 H, 8-H), 8.50 (d, J = 2.0 Hz, 1 H, 1-H), 7.20–7.80 (m, 5 H, remaining ArH), 3.82 (s, 2 H, ArCH₂S), 2.08 (s, 3 H, SCH₃). For C₁₅H₁₂OS₂ (272.4) calculated: 66.14% C, 4.44% H, 23.55% S; found: 66.30% C, 4.47% H, 23.38% S.

9-(3-Dimethylaminopropyl)-2-(methylthiomethyl)thioxanthene-9-ol (IV)

Grignard reagent was prepared by treatment of 1.82 g Mg with 8.1 g 3-dimethylaminopropyl chloride in 90 ml tetrahydrofuran using the initiation with iodine and several drops of ethyl bromide¹⁰. The solution was stirred and treated dropwise with a solution of 8.9 g II in 40 ml benzene and the mixture was refluxed for 12 h. The solvent was evaporated *in vacuo*, the residue decomposed with a saturated solution of NH₄Cl and the mixture was extracted with benzene. The extract was washed with water, dried with MgSO₄ and evaporated. The residue crystallized after mixing with light petroleum; 7.0 g (54%), m.p. 67–70°C (benzene–light petroleum). The product was identified as a 2 : 1 solvate with benzene. IR spectrum: 761, 774, 815, 847, 880 (4 and 2 adjacent and solitary Ar—H), 1 099, 1 102 (R₃C—OH in the cycle), 1 557, 1 570, 1 584, 1 595 (Ar), 2 465, 2 610, 2 670, 2 760, infl. 3 080 cm^{-1} (OH...N, N—CH₃). ¹H NMR spectrum: δ 7.00–8.00 (m, ArH), 3.65 (s, 2 H, ArCH₂S), 2.35 (s, 6 H, CH₃NCH₃), c. 2.15 (bm, 5 H, HO—C—CH₂ and CH₂N), 1.95 (s, 3 H, SCH₃). 1.20 (m, 2 H, CH₂ in the middle of the propane chain). For C₂₀H₂₅NOS₂ + 1/2 C₆H₆ (398.6) calculated: 69.30% C, 7.08% H, 3.51% N, 16.09% S; found: 69.34% C, 7.30% H, 3.26% N, 15.80% S.

9-(3-Dimethylaminopropylidene)-2-(methylthiomethyl)thioxanthene (I)

A mixture of 5.2 g IV and 100 ml 1.25M-H₂SO₄ was stirred and heated for 1 h to 100°C. After cooling it was made alkaline with NH₄OH and the base was extracted with benzene. The extract was washed with water, dried with K₂CO₃ and evaporated. The residue (4.95 g) was chromatographed on 500 g neutral Al₂O₃ (activity II). A 2 : 1 mixture of benzene and chloroform eluted first 0.4 g impurities and then 4.01 g (90%) oily I (probably a mixture of geometrical isomers). Neutralization with oxalic acid in ethanol gave 3.6 g mixture of oxalates which crystallized from a mixture of ethanol and ether; 2.4 g hydrogen oxalate, solvate with ethanol, m.p. 105–109°C, corresponding apparently to one homogeneous geometrical isomer. Mass spectrum, m/z : 341 (M⁺ corresponding to C₂₀H₂₃NS₂), 58 [CH₂=N(CH₃)₂, base peak]. For C₂₂H₂₅NO₄S₂ + C₂H₆O (477.6) calculated: 60.35% C, 6.54% H, 2.93% N, 13.43% S; found: 60.58% C, 5.97% H, 3.01% N, 13.27% S.

A sample of the pure oxalate was decomposed with NH₄OH and the pure base was isolated by extraction with ether. It was used for recording spectra. UV spectrum: $\lambda_{\max}$ 233.5 nm (log ϵ , 4.42), 272 nm (4.06), 327 nm (3.43). IR spectrum (CS₂): 742, 760 (4 adjacent Ar—H), 817, 837 (2 adjacent Ar—H), 892 cm^{-1} (solitary Ar—H in position 1). ¹H NMR spectrum: δ 7.00–7.50 (m, ArH), 5.86 (t, J = 6.0 Hz, 1 H, C=CH), 3.60 (s, 2 H, ArCH₂S), c. 2.50 (m, 4 H, CH₂CH₂N), 2.18 (s, 6 H, CH₃NCH₃), 1.95 (s, 3 H, SCH₃).

4-(Methoxymethyl)thiophenol (VI)

A) Grignard reagent was prepared by treatment of 3.2 g Mg in 80 ml tetrahydrofuran with 14.5 g 4-bromobenzyl methyl ether¹¹ and 2.6 g ethyl bromide (for maintaining the reaction in action). The mixture was stirred and refluxed for 2 h and then slowly treated with 3.2 g S which maintained the mixture for further 30 min in refluxing (without external heating). The mixture was refluxed for further 2 h, cooled and poured onto a mixture of 25 ml hydrochloric acid and 140 g ice. It was extracted with ether, the thiol was transferred by shaking with 5% NaOH into the aqueous layer, this was separated, acidified with hydrochloric acid and the purified thiol was extracted again with ether. After drying (Na_2SO_4) the extract was distilled; 7.5 g (68%), b.p. 106–108°C/2.0 kPa. For $\text{C}_8\text{H}_{10}\text{OS}$ (154.2) calculated: 62.30% C, 6.54% H, 20.79% S; found: 62.46% C, 6.65% H, 20.49% S.

B) A mixture of 10.0 g 4-bromobenzyl methyl ether¹¹, 10.6 g sodium methanethiolate and 50 ml hexamethylphosphoric triamide was stirred and heated for 5 h to 100°C and then poured onto a mixture of ice and hydrochloric acid. The product was extracted with ether and the extract processed similarly like under A; 5.1 g (65%), b.p. 106–108°C/2.0 kPa.

2,4-Dinitro-4'-(methoxymethyl)diphenyl Sulfide (VII)

A mixture of 0.30 g VI, 15 ml methanol, 3.6 ml 1M-NaOH and 0.25 g 2,4-dinitrofluorobenzene in 2.5 ml methanol was refluxed for 1 h. The product crystallized by standing overnight at room temperature; 0.30 g (48%), m.p. 76–78°C (methanol). UV spectrum: λ_{max} 328 nm ($\log \epsilon$ 4.10), 220 nm (4.43), inflexes at 266 nm (3.96) and 245 nm (4.07). IR spectrum: 810, 833 (2 adjacent Ar—H), 1095, 1110 (R—O—R'), 1335, 1510, 1585 (ArNO_2), 3080, 3110 cm^{-1} (Ar). ^1H NMR spectrum ($\text{C}^2\text{H}_3\text{SOC}^2\text{H}_3$): δ 8.90 (d, J = 2.5 Hz, 1 H, 3-H), 8.35 (q, J = 9.0; 2.5 Hz, 1 H, 5-H) 7.70 (d, J = 8.0 Hz, 2 H, 3',5'- H_2), 7.52 (d, J = 8.0 Hz, 2 H, 2',6'- H_2), 7.04 (d, J = 9.0 Hz, 1 H, 6-H), 4.55 (s, 2 H, ArCH_2O), 3.48 (s, 3 H, OCH_3). For $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_5\text{S}$ (320.3) calculated: 52.49% C, 3.78% H, 8.75% N, 10.01% S; found: 51.75% C, 3.73% H, 8.54% N, 9.60% S.

2-(4-Methoxymethylphenylthio)benzoic Acid (VIII)

VI (4.1 g), 6.6 g 2-iodobenzoic acid and 0.2 g Cu were added to a solution of 5.0 g KOH in 55 ml water. The mixture was stirred and refluxed for 7 h, filtered while hot and the filtrate was acidified with hydrochloric acid. After standing and cooling overnight the precipitate was filtered, washed with water and dried; 5.6 g (77%) crude product, m.p. 158–163°C. Analytical sample, m.p. 165–166.5°C (aqueous ethanol). UV spectrum: λ_{max} 317 nm ($\log \epsilon$ 3.67), 272 nm (3.66), 263 nm (3.97), 220 nm (4.43). IR spectrum: 750, 819 (4 and 2 adjacent Ar—H), 925, 1257, 1270, 1292, 1315, 1374, 2560, 2640, 3050 (COOH), 1555, 1585, 1598 (Ar), 1675 cm^{-1} (ArCOOH). ^1H NMR spectrum (at 60°C): δ 10.75 (bs, 1 H, COOH), 8.10 (m, 1 H, 6-H), 7.55 (d, J = 8.5 Hz, 2 H, 3',5'- H_2), 7.40 (d, J = 8.5 Hz, 2 H, 2',6'- H_2), c. 7.20 (m, 2 H, 4',5'- H_2), 6.90 (m, 1 H, 3-H), 4.51 (s, 2 H, ArCH_2O), 3.45 (s, 3 H, OCH_3). For $\text{C}_{15}\text{H}_{14}\text{O}_3\text{S}$ (274.3) calculated: 65.67% C, 5.14% H, 11.69% S; found: 65.72% C, 5.19% H, 11.74% S.

2-(4-Methoxymethylphenylthiomethyl)benzoic Acid (IX)

Na (1.15 g) was dissolved in 70 ml ethanol, 7.7 g VI and 6.7 g phthalide were added and the mixture was stirred and refluxed for 3 h. Ethanol was evaporated, the residue was diluted with 200 ml water, the mixture was filtered and the filtrate acidified with hydrochloric acid. The separated oil, which solidified by standing overnight, was filtered and crystallized from aqueous ethanol;

11.5 g (80%), m.p. 105–107°C. UV spectrum: $\lambda_{\max}$ 259 nm (log ϵ 3.94), inflexes at 280 nm (3.67), 223 nm (4.24). IR spectrum: 768, 800 (4 and 2 adjacent Ar—H), 915, 1 270, 2 520, 2 640, infl. 3 160 (COOH), 1 110 (R—O—R'), 1 485, 1 570 (Ar), **1 685** cm^{-1} (ArCOOH). ^1H NMR spectrum: δ 11.50 (bs, 1 H, COOH), 8.02 (m, 1 H, 6-H), 7.10–7.40 (m, 7 H, remaining ArH), 4.52 (s, 2 H, ArCH₂S), 4.40 (s, 2 H, ArCH₂O), 3.35 (s, 3 H, OCH₃). For C₁₆H₁₆O₃S (288.4) calculated: 66.63% C, 5.59% H, 11.12% S; found: 66.64% C, 5.65% H, 10.86% S.

2-(Methoxymethyl)thioxanthone (III)

A warm solution of 15.0 g 2-(bromomethyl)thioxanthone⁹ in 200 ml methanol was treated with a solution of 6.0 g KOH in 50 ml methanol and the mixture was refluxed for 3 h. The solvent was partly evaporated, the residue was diluted with water, the precipitated product filtered, washed with water and crystallized from 80 ml methanol; 9.2 g (77%), m.p. 77–79°C. UV spectrum: $\lambda_{\max}$ 220 nm (log ϵ 4.26), 258 nm (4.74), 280 nm (3.81), 301 nm (3.58), 382 nm (3.86). IR spectrum: 745, 825, 870 (4 and 2 adjacent and solitary Ar—H), 1 096 (R—O—R'), 1 475, 1 590 (Ar), **1 635** (ArCOAr'), 2 820 cm^{-1} (O—CH₃). ^1H NMR spectrum: δ 8.60 (m, 2 H, 1,8-H₂), c. 7.60 (m, 5 H, remaining ArH), 4.55 (s, 2 H, ArCH₂O), 3.42 (s, 3 H, OCH₃). For C₁₅H₁₂O₂S (256.3) calculated: 70.28% C, 4.72% H, 12.51% S; found: 70.28% C, 4.60% H, 12.53% S.

2-(Methoxymethyl)-9-(3-dimethylaminopropyl)thioxanthene-9-ol (V)

Grignard reagent was prepared from 1.1 g Mg and 4.9 g 3-dimethylaminopropyl chloride in 60 ml ether using a grain of iodine and 0.5 g ethyl bromide for starting the reaction. After 8 h refluxing the mixture was cooled and treated with a suspension of 5.2 g **III** in 20 ml ether, refluxed for 20 h and poured onto a mixture of ice and NH₄Cl solution. After separation of the organic layer the aqueous layer was extracted with ether and the ethereal solutions were combined. The basic product was extracted into an excess of 1 : 9 dilute hydrochloric acid, aqueous layer was made alkaline with 20% NaOH and the basic product extracted with ether. The extract was washed with water, dried (MgSO₄) and evaporated. The residue was dissolved in 10 ml toluene and treatment of the solution with light petroleum induced crystallization; 3.7 g (53%), m.p. 88.5–90.5°C (benzene–light petroleum). IR spectrum: 755, 829, 840, 860 (4 and 2 adjacent and solitary Ar—H), 1 095 (R.O.R', tertiary cyclic C—OH), 1 490, 1 560, 1 574, 1 587, 1 600 (Ar), 2 630, 2 700, 2 780, 2 820, infl. 3 100 cm^{-1} (OH...N, N—CH₃). ^1H NMR spectrum: δ 7.95 (m, 2 H, 2,8-H₂), 7.10–7.50 (m, 5 H, remaining ArH), 4.49 (s, 2 H, ArCH₂O), 3.38 (s, 3 H, OCH₃), 2.40 (s, 6 H, CH₃NCH₃), 1.90–2.40 (m, 5 H, HO—C—CH₂ and CH₂N), 1.20 (m, 2 H, CH₂ in the middle of the propane chain). For C₂₀H₂₅NO₂S (343.5) calculated: 69.93% C, 7.34% H, 4.08% N, 9.33% S; found: 69.58% C, 7.26% H, 3.65% N, 9.17% S.

4-(Phenylthio)nicotinic Acid 1-Oxide (X)

A mixture of 3.0 g 4-nitronicotinic acid 1-oxide^{14,15}, 30 ml dimethylformamide, 2.0 g thiophenol and 2.5 g K₂CO₃ was stirred for 2 h at room temperature and then for 2 h at 55–60°C. The solidified mixture was diluted with water, stirred for 10 min, washed with ether, treated with 2 ml 1 : 1 dilute hydrochloric acid and allowed to crystallize. The precipitated product was filtered and dried; 2.6 g (65%), m.p. 247–248°C with decomposition. A sample was crystallized first from 300 ml ethanol and then from dimethyl sulfoxide, m.p. 247–248°C with decomposition. UV spectrum: $\lambda_{\max}$ 340 nm (log ϵ 4.34). IR spectrum: 709, 752 (5 adjacent Ar—H in C₆H₅), 1 622 (COO[−]), 1 692, 1 730 cm^{-1} (ArCOOH). For C₁₂H₉NO₃S (247.3) calculated: 58.29% C, 3.67% H, 5.66% N, 12.97% S; found: 58.09% C, 3.81% H, 5.65% N, 13.21% S.

4-(4-Chlorophenylthio)nicotinic Acid 1-Oxide (XI)

A similar reaction of 7.9 g 4-nitronicotinic acid 1-oxide^{14,15} with 7.0 g 4-chlorothiophenol and 7.0 g K_2CO_3 in 70 ml dimethylformamide gave 10.9 g (91%) crude XI, m.p. 237–238°C with decomposition. Analytical sample, m.p. 246–247°C with decomposition (dimethyl sulfoxide and washing with methanol). IR spectrum: 670, 765 (C—Cl), 832, 855 (2 adjacent and solitary Ar—H), 945 (COOH), 1 195, 1 212 (N—O), 1 525, 1 575 (Ar), 1 695 cm^{-1} (ArCOOH). For $C_{12}H_8ClNO_3S$ (281.7) calculated: 51.16% C, 2.86% H, 12.59% Cl, 4.97% N, 11.38% S; found: 50.95% C, 3.06% H, 12.42% Cl, 4.66% N, 11.64% S.

4-(4-Chlorophenylthio)nicotinic Acid (XII)

A mixture of 3.0 g 4-chloronicotinic acid¹⁷, 5.5 g 4-chlorothiophenol and 15 ml dimethylformamide was stirred and heated for 4.5 h to 140–145°C. Most of dimethylformamide was evaporated *in vacuo*, the residue was diluted with 100 ml water, made alkaline with 20% NaOH and washed with ether. The solution was filtered with charcoal and the filtrate was slightly acidified with 1 : 3 diluted hydrochloric acid. The precipitated product was filtered after standing overnight and dried *in vacuo*; 4.1 g (81%), m.p. 220–225°C with decomposition. The analytical sample was obtained by crystallization from aqueous ethanol; monohydrate melting at 225–227°C with decomposition. UV spectrum: λ_{max} 225 nm ($\log \epsilon$ 4.44), 267 nm (4.00), 301 nm (3.96). IR spectrum: 750 (C—Cl), 803, 825 (2 adjacent Ar—H), 1 275 (COOH), 1 555 (Ar), 1 637 (COO⁻, H₂O), 3 090, 3 380 cm^{-1} (H₂O). ¹H NMR spectrum ($C^2H_3SOC^2H_3$): δ 9.06 (m, 1 H, 2-H), c. 8.45 (m, 1 H, 6-H), 7.68 (s, 4 H, ArH of 4-chlorophenylthio), 6.65 (d, J = 6.0 Hz, 1 H, 5-H). For $C_{12}H_8ClNO_2S + H_2O$ (283.7) calculated: 50.80% C, 3.55% H, 12.50% Cl, 4.94% N, 11.30% S; found: 50.83% C, 3.47% H, 12.90% Cl, 4.72% N, 11.56% S.

5,6-Dimethyl-3-(phenylthio)pyridazine-4-carbonitrile (XIII)

A mixture of 30.0 g 3-chloro-5,6-dimethylpyridazine-4-carbonitrile¹⁸, 24.8 g thiophenol, 33 g K_2CO_3 and 375 ml dimethylformamide was stirred and heated for 3.5 h to 110°C. After standing overnight the mixture was diluted with 750 ml water and extracted with chloroform. The extract was washed with water, 5% NaOH and water, dried with K_2CO_3 , filtered with charcoal and evaporated under reduced pressure. The residue was stirred with 150 ml ethanol and allowed to crystallize overnight; 33.8 g (75%), m.p. 121–124.5°C. Analytical sample, m.p. 123–125°C (ethanol). UV spectrum: λ_{max} 211.5 nm ($\log \epsilon$ 4.27), 233 nm (4.15), 258 nm (4.04), 329 nm (3.30). IR spectrum: 690, 704, 750 (5 adjacent Ar—H), 1 480, 1 560, 1 580, 3 040, 3 065 (Ar), 2 225 cm^{-1} (ArCN). ¹H NMR spectrum: δ 7.20–7.70 (m, 5 H, C₆H₅), 2.60 and 2.45 (2 s, 3 + 3 H, 2 CH₃). For $C_{13}H_{11}N_3S$ (241.3) calculated: 64.70% C, 4.59% H, 17.41% N, 13.20% S; found: 64.16% C, 4.66% H, 17.38% N, 13.37% S.

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