NEUROTROPIC AND PSYCHOTROPIC COMPOUNDS. XLVIII.*

SEVERAL DERIVATIVES OF PHENANTHRENE, ACENAPHTHENE, ANTHRACENE AND NAPHTHALENE

J.O.JÍLEK, V.SEIDLOVÁ, K.PELZ, B.KAKÁČ, J.HOLUBEK, E.SVÁTEK, Z.ŠEDIVÝ and M.PROTIVA

Research Institute of Pharmacy and Biochemistry, Prague 3

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Reaction of 10,10-dimethyl-9,10-dihydrophenanthrene-9-one (*V*), 2,2-dimethylacenaphthenone (*IX*), 10-oxospiro[anthracene-9(10*H*),1′-cyclopropane] (*XV*), 6-acetylnerolin and 6-propionylnerolin with 3-dimethylaminopropylmagnesium chloride was used for the preparation of the corresponding tertiary alcohols, the dehydration of which led in three cases to the expected olefinic bases *IV*, *XXI* and *XXII*. Dehydration of the aminoalcohol *VI* takes place under a rearrangement to the olefinic base *VII* which then splits off the dimethylaminopropane fragment, undergoing aromatization to 9,10-dimethylphenanthrene (*VIII*). Attempts at dehydration of the carbinol *XVI* also result in aromatization of the system and an opening of the cyclopropane ring; compounds *XVII*—*XX* were characterized as products. Several new 1-substituted derivatives of 2,2-dimethylacenaphthene (*XI*—*XIV*) and several potential intermediates (*XXIII*, *XXVII*, *XXVIII*) were also prepared. Compounds *III* and *VII* did not possess the expected antireserpine effect.

During the first years of development of tricyclic psychotropic agents with antipsychotic effect, a differentiation between compounds with a linearly condensed 6/6/6-skeleton (phenothiazines and analogues), characterized by central depressant and cataleptic activity and therapeutical efficacy in schizophrenic psychoses, and between compounds with a linearly condensed 6/7/6-skeleton (dibenzo[*a*,*d*]cycloheptenes and analogues) with antireserpine and thymoleptic activity for treatment of depressive psychoses, was clearly indicated[1]. The first inconsistency with this regular pattern appeared upon finding antireserpine and antidepressant activity in 9-(3-dimethylaminopropylidene)-10,10-dimethyl-9,10-dihydroanthracene (*I*) ("melitracene")[2,3] and in 10-(3-dimethylaminopropyl)-9,9-dimethylacridane (*II*) ("dimethacrine")[4,5]. The structure of these two compounds brought us to formulating the structures of the hitherto undescribed compounds *III* and *IV* in which a psychotropic

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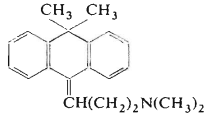
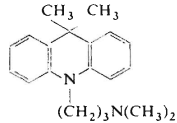
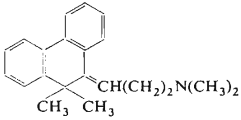
activity was to be expected. The main object of the present work are synthetic experiments aiming at the preparation of compounds *III* and *IV*.



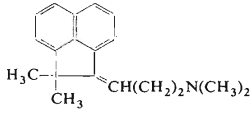
I



II



III

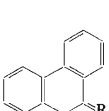


IV

In the 9,10-dihydrophenanthrene series,* the starting compound was 10,10-dimethyl-9(10*H*)phenanthrone (*V*)[6-8] which reacted with 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran[9] to a high yield of 9-(3-dimethylaminopropyl)-10,10-dimethyl-9,10-dihydro-9-phenanthrol (*VI*). This tertiary alcohol does not readily eliminate water since it produces a stable crystalline hydrochloride; when attempting dehydration by boiling with acetyl chloride in chloroform it is recovered unchanged. Dehydration is achieved only by several hours' refluxing with phosphorus oxychloride. Two products are then formed: the base $C_{21}H_{25}N$, the empirical formula of which corresponds to the desired olefinic base *III*, and further hydrocarbon $C_{16}H_{14}$. A closer investigation of the basic product, particularly its IR and NMR spectra, excluded, however, structure *III* and the compound was defined as the isomeric 9-(3-dimethylaminopropyl)-9-methyl-10-methylene-9,10-dihydrophenanthrene (*VII*). The main argument for this definition were the two singlets in the NMR spectrum at 5·40 and 5·26δ corresponding to two protons of the $C{=}CH_2$ group. The hydrocarbon was identified as 9,10-dimethylphenanthrene (*VIII*) (ref.[6,10-12]). It is assumed that, first of all, the corresponding 9-substituted 10,10-dimethyl-9,10-dihydrophenanthrylium cation is formed which is stabilized by rearrangement to the olefin *VII*. Subsequent cleavage and aromatization of this compound gives rise to the hydrocarbon *VIII*. A similar reaction sequence was described by Shriner and Geipel[13] for acid-catalyzed transformations of 9-phenyl-10,10-dimethyl-9,10-dihydro-9-phenanthrol. We did not confirm the identity of the aliphatic fragment which accompanies the

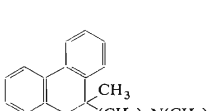
* Experiments in the 9,10-dihydrophenanthrene series were carried out in this Laboratory in 1964 by Dr I. Ernest.

formation of the hydrocarbon *VIII* but we assume that it is 3-dimethylaminopropyl chloride.

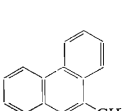


V, R = O

VI, R = $\langle^{OH}_{(CH_2)_3N(CH_3)_2}$

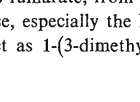


VII



VIII

In the acenaphthene series we proceeded from 2,2-dimethyl-1-acenaphthenone (*IX*) which was recently prepared by methylation of acenaphthenone[14]. Reaction with 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran[9] yielded the oily aminoalcohol *X* which was gently neutralized with hydrogen chloride in ether to give crystalline hydrochloride. Otherwise, alcohol *X* is dehydrated quite readily; on a preparative scale it was done by boiling with ethanolic hydrogen chloride. The resulting base is probably a mixture of geometric isomers which accounts for the lack of success of attempts at preparation in crystalline form. One of the isomers was purified by crystallizing it as fumarate, from which the base was liberated and characterized by spectra. Of these, especially the NMR spectrum supports unequivocally the identity of the product as 1-(3-dimethylaminopropylidene)-2,2-dimethylacenaphthene (*IV*).



IX, R = O

X, R = $\langle^{OH}_{(CH_2)_3N(CH_3)_2}$

XI, R = $\langle^{H}_{OH}$

XII, R = $\langle^{H}_{O(CH_2)_2N(CH_3)_2}$

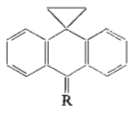
XIII, R = $\langle^{H}_{Cl}$

XIV, R = 

Reduction of ketone *IX* with sodium borohydride yielded 2,2-dimethyl-1-acenaphthenol (*XI*) which was treated with sodium amide and 2-dimethylaminoethyl chloride and converted to the basic ether *XII*. By treatment with hydrogen chloride in benzene at room temperature, alcohol *XI* yielded an oily and distillable 2,2-dimethyl-1-chlor-

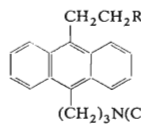
acenaphthene (*XIII*). This chloro derivative, the structure of which has been determined by its NMR spectrum, was found to have low reactivity in attempting a substitution reaction with 1-methylpiperazine. After boiling the reaction components several hours, only 20% of nonuniform basic product was obtained, from which the desired substitution product *XIV* was isolated in a small amount only as crystalline picrate. Its formation is accompanied by that of another unidentified basic product.

We attempted further to prepare the spirocyclopropane analogue of compound *I*, proceeding from 10-oxospiro[anthracene-9(10*H*),1'-cyclopropane] (*XV*) which is available through the reaction of 10-methyleneanthrone with diazomethane[15]. This ketone reacts in the usual way with 3-dimethylaminopropylmagnesium chloride, yielding the crystalline 10-(3-dimethylaminopropyl)-10-hydroxyspiro[anthracene-9(10*H*),1'-cyclopropane] (*XVI*). If one uses for the isolation of the basic product extraction with dilute hydrochloric acid, a different transformation of the primary product *XVI* takes place. A yellow base $C_{21}H_{24}ClN$ is obtained; according to its UV spectrum it is a fully aromatic anthracene derivative which is formulated as *XVII*. The chlorine atom in this compound has low reactivity since the compound does not change upon heating with 3·5M methanolic potassium hydroxide or on heating with a benzene solution of 1-methylpiperazine. Aromatization and opening of the cyclopropane ring occur when attempting dehydration of alcohol *XVI* by heating with acetic anhydride. Here, too, a yellow crystalline base with an anthracene chromophor is obtained, the structure of which is probably 9-(3-dimethylaminopropyl)-10-(2-acetoxyethyl)anthracene (*XVIII*). When attempting a gentle dehydration of alcohol *XVI* by short heating with anhydrous oxalic acid in acetic acid or by heating with maleic acid in aqueous solution, oily products were obtained, from which only after distillation we succeeded in preparing a crystalline red picrate. Its analysis indicates the same composition of the base as that of the starting alcohol *XVI*. In these cases, too, we assume aromatization to the anthracene derivative *XIX*. An analogous aromatization apparently occurs during the preparation of picrate of amine *XVI* through the reaction with picric acid in boiling ethanol. The orange picrate obtained reppresents a homologue higher by C_2H_4 – this is explained as due to solvolysis to the anthracene derivative *XX*. Our findings are thus in agreement with those of Eberson and coworkers[16]



XV, R = O

XVI, R = 



XVII, R = Cl

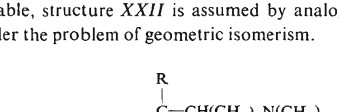
XVIII, R = $OCOCH_3$

XIX, R = OH

XX, R = OC_2H_5

who describe interconversions of compounds of the type of 10-hydroxyspiro[anthracene-9(10*H*),1′-cyclopropane] and 9-(2-hydroxyethyl)anthracene *via* the corresponding anthrylethyl bridged cation, the existence of which was demonstrated by its NMR spectrum[17].

Finally, reaction with 3-dimethylaminopropylmagnesium chloride was tested with two ketones of the naphthalene series, *viz.* 6-acetylnerolin[18,19] and 6-propionylnerolin[20]. In both cases, the basic products were isolated by extraction into dilute hydrochloric acid. During this process a dehydration took place which was then completed by heating with dilute sulfuric acid. The corresponding unsaturated bases resulted, possessing a double bond in conjugation with the naphthalene ring (UV spectra), the first of which was identified as *XXI* (because of the absence of the band at 885–895 cm^{-1} in the IR spectrum). For the second base, where such proof is not available, structure *XXII* is assumed by analogy. In none of the two cases did we consider the problem of geometric isomerism.

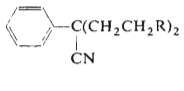


XXI, R = CH_3
XXII, R = C_2H_5

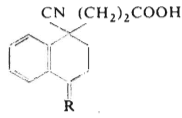
XXIII

In the experimental section we describe further the preparation and characterization of *XXIII*–*XXVIII* as potential intermediates for further work. 5-Methoxy-2-tetralone (*XXIII*) was prepared as described before[21] and characterized as oxime, semicarbazone and 2,4-dinitrophenylhydrazone. The ketone itself is apparently so enolized that its reaction with 3-dimethylaminopropylmagnesium chloride and subsequent hydrolysis with dilute hydrochloric acid result in a practically quantitative recovery of the starting compound. For transformation of the dinitrile of γ-phenyl-γ-cyanopimelic acid (*XXIV*)[22] to γ-phenyl-γ-cyanopimelic acid (*XXV*), it was found suitable to use the now described hydrolysis with concentrated hydrochloric acid rather than the previously described alkaline hydrolysis[23]. The acid *XXV* was cyclized to 4-cyano-4-(2-carboxyethyl)-1-tetralone (*XXVI*) according to literature data[23], using sulfuric acid, as well as in contradiction with the same data[23] using polyphosphoric acid or as crude chloride with aluminium chloride – even if in low yields. From the tetralone derivative *XXVI* the oxo group was removed by hydrogenation on palladium in acetic acid in the presence of perchloric acid; the resulting acid was 3-(1-cyano-1-tetralyl)propionic acid (*XXVII*). Alkylation of phenylacetonitrile with 4-chlorobutyronitrile[24] yielded α-phenyladiponitrile (*XXVIII*) (see also ref.[25–27]).

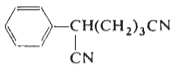
Compounds *IV*, *VII*, *XII*, *XXI* and *XXII* were evaluated pharmacologically in the form of the corresponding salts (*VII*, *XXI* and *XXII* as hydrochlorides, *IV* as hydrogenfumarate, *XII* as hydrogenmaleate) by Dr J. Metyšová at the pharmacological department of this institute (mainly from the point of view of neurotropic effects) and by Dr F. Hradil of the affiliated unit of this institute at Rosice n.L. (by methods of general pharmacological screening). They were also tested by Dr J. Turinová at the bacteriological department of this institute (headed by Dr A. Šimek) as to their inhibitory activity against several microbial species *in vitro*.



XXIV, R = CN
XXV, R = CO_2H



XXVI, R = O
XXVII, R = H_2



XXVIII

Compound *VII* was applied intravenously (LD_{50} for mice was 36 mg/kg). In a dose of 12 mg/kg it shows a slight activity in the rotating-rod test in mice, it decreases slightly the body temperature of rats and brings about a slight and protracted drop of blood pressure in rats. In the dose shown it displayed a certain cataleptic effect in rats but had no antireserpine effect in mice (ptosis, rectal temperature). In the *in vitro* test (rat duodenum) it displayed a certain spasmolytic antiacetylcholine effect. At concentrations of 50 μg/ml, *VII* inhibits the growth of *Streptococcus* β-*haemolyticus*, *Staphylococcus pyogenes aureus* (including its penicillin-resistant strain) and *Mycobacterium tuberculosis* $H_{37}Rv$. Compound *IV* was also applied intraveneously (LD_{50} 45·5 mg/kg). In the rotating-rod test in mice it brings about a disturbance of motor coordination only in subtoxic doses. On the other hand, it potentiates thiopental narcosis of mice from 2·5 mg/kg. At a dose of 10 mg/kg *i.p.* it brings about catalepsy in 30% of rats. It showed no antiserotonin effect on rats *in vivo*, no antireserpine effect in the ptosis test on mice (10 mg/kg *i.p.*) and no antihistamine effect in the aerosol or detoxication test in guinea-pigs (5 mg/kg and 1 mg/kg, respectively). At a concentration of 12·5 μg/ml it inhibits growth of *M. tuberculosis* $H_{37}Rv$.

Parenterally applied compound *XII* (LD_{50} 54 mg/kg) is practically ineffective in the rotating-rod test; it potentiates thiopental narcosis of mice from 5 mg/kg, in 20% rats it causes catalepsy at a dose of 10 mg/kg *i.p.* and has no antiserotonin, antireserpine and antihistamine activity. Compounds *XXI* and *XXII* displayed only a structurally nonspecific local anaesthetic and spasmolytic activity.

On the whole, it should be stated that the central depressant activity of the compounds prepared is rather low and that the expected antireserpine activity is totally absent.

EXPERIMENTAL

The melting points of analytical preparations were estimated in Kofler's block. The samples were dried for 8 h *in vacuo* (about 0·2 Torr) over phosphorus pentoxide at a temperature adequate to the melting point of the compound (100°C at most). The UV spectra (methanol) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra in a Unicam SP 200G spectrophotometer and the NMR spectra (deuteriochloroform) in a ZKR 60 spectrometer (Zeiss-Jena) (using hexamethyldisiloxane as reference standard, the values shown referring to tetramethylsilane).

10,10-Dimethyl-9(10*H*)-phenanthrone (*V*)

It was obtained in a 77% yield by heating 9,10-dimethyl,9-10-dihydroxy-9,10-dihydrophenanthrene with sulfuric acid in acetic acid in principle according to the literature data[6–8]. If the crude product (residue) was left to crystallize spontaneously, a modification with a higher melting point 73—75°C was obtained, as described by some authors[6,7]. On the other hand, the redistilled product (b.p. 170°C/4 Torr) solidifies to a lower melting modification (m.p. 61—62°C) which was described by French authors[8] after this work had been finished.

9-(3-Dimethylaminopropyl)-10,10-dimethyl-9,10-dihydro-9-phenanthrol (*VI*)

A solution of 15·5 g ketone *V* in 80 ml tetrahydrofuran was added dropwise under stirring to a solution of 3-dimethylaminopropylmagnesium chloride[9] which had been prepared from 17·1 g 3-dimethylaminopropyl chloride and 3·0 g magnesium in 80 ml tetrahydrofuran (initiated with iodine and ethyl bromide). The mixture was stirred and refluxed for 4 h and, after cooling overnight, decomposed with 15% ammonium chloride. Extraction with benzene, drying of the extract with sodium sulfate and evaporation yielded 20·2 g oily product. Chromatography of a sample (1·0 g) on a column of 30 g alumina (activity II) and elution with chloroform produced a crystalline compound (0·7 g) which was used for inoculating the main portion: m.p. 75—76°C (light petroleum). UV spectrum: λ_{max} 214 nm (log ε 4·512), 270 nm (4·183). IR spectrum (KBr): 759, 765 (1,2-disubstituted benzene), 2781 and 2813 (dimethylamino), 3425 cm^{-1} (OH). For $C_{21}H_{27}NO$ (309·4) calculated: 81·51% C, 8·80% H, 4·43% N; found: 81·39% C, 8·65% H, 4·52% N.

Hydrochloride-monohydrate, m.p. 205—205·5°C (ethanol–ether). For $C_{21}H_{30}ClNO_2$ (363·9) calculated: 69·31% C, 8·31% H, 9·74% Cl, 3·85% N; found: 68·99% C, 8·20% H, 9·92% Cl, 4·28% N.

9-(3-Dimethylaminopropyl)-9-methyl-10-methylene-9,10-dihydrophenanthrene (*VII*)

A mixture of 19·6 g alcohol *VI* and 200 ml phosphorus oxychloride was refluxed for 4 h. The phosphorus oxychloride was then evaporated, the residue decomposed with dilute sodium hydroxide and extracted with benzene. Evaporation of the extract yielded 16·7 g oil which was dissolved in 25 ml ethanol. On cooling, 3·6 g crystalline neutral product, melting at 147°C (ethanol–benzene), precipitated and was identified as 9,10-*dimethylphenanthrene* (VIII). The literature data[6,10–12] give m.p. from 139 to 144°C. UV spectrum: λ_{max} 253·5 nm (log ε 4·804), 297·5 nm (4·047). IR spectrum (KBr): 722 and 755 (9,10-disubstituted phenanthrene), 1433 (CH_3), 1605 cm^{-1} (Ar). For $C_{16}H_{14}$ (206·3) calculated: 93·16% C, 6·84% H; found: 92·90% C, 7·09% H.

The mother liquor after the neutral product was partly evaporated, diluted with ether and, by adding a slight excess of a solution of anhydrous hydrogen chloride in ether, the *hydrochloride* of the basic product was obtained: 13·0 g, m.p. 209—212°C, under decomposition. When checking the sample by thin-layer chromatography on silica gel, the product appears to be homogeneous but its m.p. gradually rises on crystallization from ethanol–ether up to 249—250·5°C. UV spectrum: λ_{max} 217 nm (log ε 4·502), 240 nm (4·354), 246·5 nm (4·370), 282 nm (4·115). IR spectrum

(KBr): very strong band 740 (1,2-disubstituted benzene), strong band 908 (RR'C=CH_2), 1449 (CH_3), 1623 (C=C conjugated), 2435 cm^{-1} (NH^+Cl^-). NMR spectrum: δ about 12·00 (1 H of HCl), 7·10—8·00 (multiplet, 8 H of aromatic rings), 5·40 and 5·26 (2 singlets, 2 H of the =CH_2 group), 2·58 (singlet, 6 H in $N(CH_3)_2$), about 2·50 (2 H in NCH_2), 1·62 (singlet, 3 H in C—CH_3), 1·44 (multiplet, 4 H in C—CH_2CH_2—C). For $C_{21}H_{26}ClN$ (327·9) calculated: 76·92% C, 7·99% H, 10·81% Cl, 4·27% N; found: 76·36% C, 8·16% H, 10·58% Cl, 4·45% N.

1-(3-Dimethylaminopropyl)-2,2-dimethylacenaphthenol (*X*)

A solution of 10·8 g 2,2-dimethylacenaphthenone (*IX*) (b.p. 109—110°C/0·7 Torr, m.p. 71—72°C) (ref.[14]) in 35 ml tetrahydrofuran was added dropwise under stirring over a period of 30 min to a solution of 3-dimethylaminopropylmagnesium chloride[9] prepared by a reaction of 8·4 g 3-dimethylaminopropyl chloride with 1·75 g magnesium in 80 ml tetrahydrofuran (initiated by iodine and ethylene dibromide). The mixture was refluxed for 4 h, left to stand overnight and decomposed with a 7% solution of ammonium chloride and extracted with benzene. The extract was concentrated to about 100 ml, cooled, and extracted twice with 30 ml 0·65M-H_2SO_4. The acid aqueous solution was separated, immediately made alkaline with 2·5M-NaOH and the liberated base was isolated by extraction with ether: 8·5 g (54%), viscous oil.

Hydrochloride-hemihydrate, m.p. 124—126°C (ethanol–ether). For $C_{19}H_{26}ClNO.0{\cdot}5\ H_2O$ (328·9) calculated: 69·30% C, 8·27% H, 10·75% Cl, 4·25% N; found: 69·00% C, 8·27% H, 10·52% Cl, 3·96% N.

1-(3-Dimethylaminopropylidene)-2,2-dimethylacenaphthene (*IV*)

A slight excess of ethanolic hydrogen chloride was added to a solution of 5·8 g alcohol *X* in 40 ml ethanol and the mixture was refluxed for 1 h. The solvents were then evaporated under reduced pressure and the base was liberated from the residue by alkalinization. Then it was extracted with ether: 4·4 g (81%). Neutralization with fumaric acid in ethanol yielded the *hydrogen fumarate*, m.p. 132—134°C (ethanol–ether). For $C_{23}H_{27}NO_4$ (381·5) calculated: 72·42% C, 7·13% H, 3·67% N; found: 72·06% C, 7·29% H, 3·50% N.

Alkalinization and extraction with ether yielded the oily base. UV spectrum: λ_{max} 238 nm (log ε 4·570), 290 nm (3·995), 311 nm (4·133), 317 nm (4·045), 327 nm (4·009), 334 nm (3·966). IR spectrum (Nujol): 780 (1,2,3-trisubstituted benzene), 831, 1027, 1043, 1099, 1179, 1268, 1589, 1600, 1616, 2720 cm^{-1}. NMR spectrum: δ 1·40 (singlet, 6 H of CH_3—C—CH_3), 2·30 (singlet, 6 H of CH_3NCH_3), 2·40—3·00 (multiplet, 4 H in CH_2 groups), 5·75 (triplet, 1 H in C=CH), 7·00—8·00 (multiplet, 6 H of aromatic rings).

2,2-Dimethyl-1-acenaphthenol (*XI*)

Two ml of a 10% solution of sodium hydroxide were added to a solution of 67·3 g 2,2-dimethylacenaphthenone in 750 ml ethanol and followed quickly under stirring with 16·0 g sodium borohydride. The mixture was refluxed for 35 min on a boiling water bath, ethanol was removed by distillation and the residue dissolved in 750 ml chloroform. The solution was washed with water, dried with potassium carbonate and evaporated. The residue was crystallized from light petroleum: 57·6 g (84%), m.p. 76·5°C (needles). This form on further crystallization changed its shape (prisms) as well as m.p. to 92°C. Apparently two crystal modifications are involved. UV spectrum: λ_{max} 225 nm (log ε 4·812). 276 nm (3·770), 285 nm (3·831), 296 nm (3·694). IR spectrum (Nujol): 778 and 792 (1,2,3-trisubstituted benzene), 1608 and 1620 (Ar), 1087 and

3380 cm^{-1} (OH). NMR spectrum: δ 1·33—1·43 (doublet, 6 H of C-methyl groups), 1·97 (singlet, 1 H of the OH group, disappears after deuterization), 5·10 (singlet, 1 H of CH—O—), 7·05 to 7·85 (multiplet, 6 H of aromatic rings). For $C_{14}H_{14}O$ (198·3) calculated: 84·81% C, 7·12% H; found: 85·00% C, 7·15% H.

1-(2-Dimethylaminoethoxy)-2,2-dimethylacenaphthene (*XII*)

8·3 g alcohol *XI* was added to a suspension of 3·0 g sodium amide in 50 ml benzene and the mixture was stirred for 15 min, 5·5 g 2-dimethylaminoethyl chloride was then added and the mixture refluxed for 8 h. After cooling, it was decomposed with water and diluted with benzene, the benzene layer was dried and distilled: 8·7 g (77·6%), b.p. 159—161°C/1·6 Torr. UV spectrum: λ_{max} 225 nm (log ε 4·842), 268·5 nm (3·736), 277 nm (3·863), 287 nm (3·910), 297 nm (3·746). IR spectrum (Nujol): 780 (1,2,3-trisubstituted benzene), 1117 (C—O—C), 1610 and 1622 (Ar), 2775 and 2825 cm^{-1} (dimethylamino) NMR spectrum: δ 6·90—7·90 (multiplet, 6 H of aromatic rings), 4·82 (singlet, 1 H at C-1 of the skeleton), 3·83 (triplet, 2 H of $—OCH_2—$), 2·53 (triplet, 2 H of $—CH_2N—$), 2·21 (singlet, 6 H of N-methyl groups), 1·40 and 1·33 (2 singlets, 6 H of C-methyl groups). For $C_{18}H_{23}NO$ (269·4) calculated: 80·25% C, 8·61% H, 5·20% N; found: 79·92% C, 8·60% H, 5·06% N.

Picrate, m.p. 142—144°C (ethanol). For $C_{24}H_{26}N_4O_8$ (498·5) calculated: 57·82% C, 5·26% H, 11·24% N; found: 57·52% C, 5·32% H, 11·35% N.

As it was not possible to prepare salts with pharmacodynamically unobjectionable acids (hydrochloride, maleate, salicylate) in crystalline state we prepared a greater amount of analytically pure picrate which was decomposed by filtering its acetone solution through a column of alumina. The base thus liberated was converted to an aqueous solution of maleate which was then used for testing.

1-Chloro-2,2-dimethylacenaphthene (*XIII*)

5 g anhydrous powdery calcium chloride was added to a solution of 5·2 g alcohol *XI* in 50 ml benzene and the mixture was saturated with anhydrous hydrogen chloride. After standing at room temperature overnight, the mixture was filtered, the filtrate washed with water, dried and evaporated. The residue was distilled to obtain 4·5 g product boiling at 118—119°C/0·5 Torr which, according to a gas chromatography check, is practically uniform. NMR spectrum: δ 1·49 (singlet, 6 H of C-methyl groups), 5·42 (singlet, 1 H of CHCl), 7·00—7·90 (multiplet, 6 H of aromatic rings). For $C_{14}H_{13}Cl$ (216·7) calculated: 77·59% C, 6·05% H, 16·36% Cl; found: 77·68% C, 6·20% H, 16·09% Cl.

1-(4-Methylpiperazino)-2,2-dimethylacenaphthene (*XIV*)

A mixture of 7·3 g 1-chloro-2,2-dimethylacenaphthene (*XIII*) and 10·0 g 1-methylpiperazine was refluxed for 5 h in a 110—115°C bath. After cooling, it was decomposed with 100 ml water and extracted with 100 ml benzene. From the benzene layer, which was washed with water, the basic product was extracted with 70 ml 3M-HCl. As a neutral fraction, distillation of the benzene solution recovered 4·8 g of the chloride *XIII*, b.p. 120—122°C/0·9 Torr. Its identity was proved by analysis and by NMR spectrum. Alkalinization of the acid aqueous layer with aqueous ammonia and extraction with benzene yielded 1·77 g (19%) oily nonhomogeneous base. This was converted in the usual way in ethanol to picrate which crystallized in the form of two clearly distinguished crystal types which were separated mechanically: spherical druses with m.p. equal to 195—200°C and prisms melting at 176—178°C. Recrystallization of the higher-melting frac-

tion from ethanol finally yielded a product melting at 216–218°C, its analysis corresponding to expectation. For $C_{25}H_{27}N_5O_7$ (509·5) calculated: 58·93% C, 5·34% H, 13·75% N; found: 58·77% C, 5·33% H, 13·48% N.

10-(3-Dimethylaminopropyl)-10-hydroxyspiro[anthracene-9(10*H*), 1'-cyclopropane] (*XVI*)

A solution of 8·0 g 10-oxospiro[anthracene-9(10*H*),1'-cyclopropane] (*XV*) (m.p. 151–155°C)[15] in 50 ml tetrahydrofuran was added dropwise to a solution of 3-dimethylaminopropylmagnesium chloride[9] which was prepared by a reaction of 6·7 g 3-dimethylaminopropyl chloride with 1·3 g magnesium in 40 ml tetrahydrofuran (initiation with iodine and 0·1 ml ethyl bromide). The mixture was refluxed under stirring for 4 h. After standing overnight it was decomposed with a saturated solution of ammonium chloride, the aqueous phase was separated and extracted with benzene. The combined organic phases were evaporated, the residue was dissolved in a mixture of benzene and chloroform, the solution washed with water, dried with potassium carbonate and evaporated again. The residue was dissolved in 15 ml ether and crystallization was induced by the addition of light petroleum; 5·9 g (53%), m.p. 123–124°C (benzene–light petroleum). UV spectrum: λ_{max} 213·5 nm (log ε 4·336), 265 nm (3·137), 272 nm (3·086). IR spectrum (Nujol): 760 and 771 (1,2-disubstituted benzene), 1 040 (OH), 1 600 cm^{-1} (Ar). For $C_{21}H_{25}NO$ (307·4) calculated: 82·04% C, 8·20% H, 4·56% N; found: 82·30% C, 8·20% H, 4·46% N.

9-(3-Dimethylaminopropyl)-10-(2-chloroethyl)anthracene (*XVII*)

Solution of 3-dimethylaminopropylmagnesium chloride was prepared by a reaction of 13·3 g 3-dimethylaminopropyl chloride with 2·6 g magnesium in 40 ml ether (initiation with iodine and ethyl bromide, the mixture refluxed for 3 h). A solution of 16·0 g ketone *XV* in 150 ml tetrahydrofuran and 100 ml benzene was added to it dropwise at room temperature under stirring. After 4 h of refluxing, it was processed as in the preceding case. To isolate the basic fraction the solution of the crude product in benzene was shaken with 15% hydrochloric acid. A total of 16·1 g yellow hydrochloride precipitated (m.p. 206–209°C). Decomposition of this hydrochloride with a solution of sodium hydroxide and extraction with ether yielded a yellow base, melting at 94°C (ethanol). UV spectrum: λ_{max} 219·5 nm (log ε 4·193), 258·5 nm (5·287), 249 nm (inflexion) (4·944), 338 nm (3·522), 354 nm (3·868), 375 nm (4·102), 395 nm (4·115). IR spectrum (Nujol): 728, 759, 848, 1 037, 1 046, 1 240, 1 367, 1 379, 1 622 cm^{-1}. For $C_{21}H_{24}ClN$ (325·9) calculated: 77·40% C, 7·42% H, 10·88% Cl, 4·30% N; found: 77·35% C, 7·47% H, 10·72% Cl, 4·22% N.

Hydrochloride-monohydrate, m.p. 210–213°C (ethanol). For $C_{21}H_{27}Cl_2NO$ (380·4) calculated: 66·31% C, 7·15% H, 18·64% Cl, 3·68% N; found: 66·77% C, 7·16% H, 19·00% Cl, 3·77% N.

Hydrogen maleate, m.p. 169°C (ethanol–ether). For $C_{25}H_{28}ClNO_4$ (442·0) calculated: 67·94%C, 6·39% H, 8·02% Cl, 3·17% N; found: 67·75% C, 6·50% H, 7·90% Cl, 3·15% N.

9-(3-Dimethylaminopropyl)-10-(2-acetoxyethyl)anthracene (*XVIII*)

A mixture of 1·8 g alcohol *XVI* and 20 ml acetic anhydride was refluxed for 4 h under stirring in a bath at 160°C. After cooling, 20 ml water were added, the mixture was heated until acetic anhydride decomposed, and evaporated at reduced pressure. The residue was dissolved in water, the solution was washed with ether, the base was liberated by alkalinization and isolated by extraction with ether; 1·4 g yellow crystals melting at 93–94°C (light petroleum). UV spectrum: λ_{max} 218 nm (log ε 4·172), 222 nm infl. (4·148), 251 nm (4·954), 258 nm (5·242), 339 nm (3·496), 356 nm (3·837), 374·5 nm (4·070), 395 nm (4·079). IR spectrum (Nujol): 771 (1,2-disubstituted

benzene), 1249 and 1732 (—COO—) cm^{-1}. For $C_{23}H_{27}NO_2$ (349·5) calculated: 79·05% C, 7·79% H, 4·01% N; found: 79·49% C, 8·03% H, 4·13% N.

Hydrochloride-monohydrate, m.p. 186—187°C (aqueous acetone-ethanol). UV and IR spectra of the product correspond to those of the base. The IR spectrum (Nujol) displays bands at 3 438 and 3 481 cm^{-1} which are attributed to the presence of crystal water. For $C_{23}H_{30}ClNO_3$ (404·0) calculated: 68·38% C, 7·49% H, 8·78% Cl, 3·47% N: found 68·35% C, 7·48% H, 9·01% Cl, 3·40% N.

9-(3-Dimethylaminopropyl)-10-(2-hydroxyethyl)anthracene (*XIX*)

A. *From oxalic acid in acetic acid*: A mixture of 0·75 g alcohol *XVI*, 1·09 g anhydrous oxalic acid and 5·5 ml acetic acid was refluxed for 30 s. After cooling, it was diluted with 100 ml water, the solution was made alkaline and extracted with benzene. Evaporation of the extract produced 0·7 g oil which was first chromatographed on a column of 21 g alumina and the main fraction obtained by evaporation of the benzene eluate (0·5 g) was redistilled in high vacuum from a collar flask. The distillate (0·15 g) was converted to picrate in the usual way, m.p. 165—167°C (ethanol–acetone). For $C_{27}H_{28}N_4O_8$ (536·5) calculated: 60·44% C, 5·26% H, 10·44% N; found: 60·26% C, 5·45% H, 10·69% N.

B. *From maleic acid in water*: A solution of 0·6 g alcohol *XVI* and 0·2 g maleic acid in 10 ml water was heated for 1 h to 100°C. After cooling the solution (a small amount of insoluble oil having been separated) was evaporated at reduced pressure, the base was liberated from the residue by alkalinization and isolated by extraction with ether (0·4 g). Similarly to the preceding case, it was redistilled and converted to the picrate (red crystals), m.p. 167°C (ethanol). For $C_{27}H_{28}.N_4O_8$ (536·5) calculated: 60·44% C, 5·26% H, 10·44% N; found: 60·35% C, 5·54% H, 10·93% N.

9-(3-Dimethylaminopropyl)-10-(2-ethoxyethyl)anthracene (*XX*)

Alcohol *XVI* (0·2 g) was neutralized with picric acid (0·15 g) in 10 ml boiling ethanol. A total of 0·2 g orange *picrate* was obtained which recrystallized from a mixture of ethanol and acetone and melted at 99—102°C. For $C_{29}H_{32}N_4O_8$ (564·6) calculated: 61·69% C, 5·71% H, 9·92% N; found: 61·16% C, 5·75% H, 9·71% N.

2-(6-Methoxy-2-naphthyl)-5-dimethylamino-2-pentene (*XXI*)

The reaction of 3-dimethylaminopropylmagnesium chloride (from 36·0 g 3-dimethylaminopropyl chloride and 6·24 g magnesium in 120 ml tetrahydrofuran) with 40 g 6-acetylnerolin (m.p. 104—106°C) (refs[18,19]) in 130 ml tetrahydrofuran was carried out as in the preceding cases. The reaction mixture was decomposed with 10% ammonium chloride and extracted with ether. The basic product was extracted from the ether extract with excess 5M-HCl whence it was liberated by alkalinization and then isolated by extraction with ether. In this way, a total of 36 g crude product was obtained, a sample of which was used for the preparation of the hydrochloride. The salt composition indicated that we are dealing here with a mostly dehydrated substance. For this reason, the whole amount of the product was refluxed for 1 h with dilute sulfuric acid (20 ml sulfuric acid and 180 ml water). After cooling, the solution obtained was made alkaline with aqueous ammonia, the base was isolated by extraction with ether and, after evaporation of the extract, it was converted by an ether solution of hydrogen chloride to the *hydrochloride*. To purify it to constant m.p. (233—234°C) it had to be recrystallized several times from ethanol–ether. UV spectrum had maxima at 242 and 285 nm. IR spectrum (Nujol): 838 ($R_2C{=}CHR$),

1 250 ($ArOCH_3$), 1 503 and 1 605 (Ar), 1 630 (C=C in conjugation), 2 500 cm^{-1} (N···HCl). For $C_{18}H_{24}ClNO$ (305·8) calculated: 70·69% C, 7·91% H, 11·59% Cl, 4·58% N; found: 70·61% C, 8·09% H, 11·77% Cl, 4·84% N.

3-(6-Methoxy-2-naphthyl)-6-dimethylamino-3-hexene (*XXII*)

Similarly to the preceding case, reaction of 31·5 g 6-propionylnerolin (m.p. 108–110°C)[20] with 3-dimethylaminopropylmagnesium chloride (from 27 g 3-dimethylaminopropyl chloride) and subsequent treatment yielded 25 g of a crude hydrochloride, the dehydration of which was completed by heating with dilute sulfuric acid (20 ml sulfuric acid and 180 ml water). The crude base obtained in the usual way (19 g) was converted to the *hydrochloride*, crystallizing as *hemihydrate*; m.p. 199–201°C (ethanol–ether). IR spectrum (Nujol): 850 ($R_2C{=}CHR$), 1 253 (Ar. $.OCH_3$), 1 606 (Ar), 1 624 (C=C–Ar), 2 600 (N..HCl), 3 500 cm^{-1} (H_2O). For $C_{19}H_{26}ClNO$. $.0.5\,H_2O$ (328·9) calculated: 69·39% C, 8·27% H, 10·78% Cl, 4·26% N; found: 69·54% C, 8·04% H, 10·62% Cl, 4·34% N.

5-Methoxy-2-tetralone (*XXIII*)

This was prepared by reduction of 1,6-dimethoxynaphthalene with sodium and ethanol according to a described procedure[21] in a 62% yield, b.p. 138–145°C/4 Torr.

Oxime was obtained in the usual way by reaction of the ketone with hydroxylamine hydrochloride and sodium acetate in boiling aqueous ethanol, m.p. 129–132°C (ethanol). For C_{11}. $.H_{13}NO_2$ (191·2) calculated: 69·09% C, 6·85% H, 7·33% N; found: 69·40% C, 7·07% H, 7·39% N.

Semicarbazone was prepared in a similar way using semicarbazide hydrochloride; m.p. 144–146°C (ethanol). For $C_{12}H_{15}N_3O_2$ (233·3) calculated: 61·78% C, 6·48% H, 18·02% N; found: 62·26% C, 6·61% H, 18·26% N.

2,4-*Dinitrophenylhydrazone*, m.p. 187–189°C (ethyl acetate). For $C_{17}H_{16}N_4O_5$ (356·3) calculated: 57·30% C, 4·53% H, 15·72% N; found: 56·99% C, 4·62% H, 15·35% N.

γ-Phenyl-γ-cyanopimelic Acid (*XXV*)

A mixture of 11·4 g dinitrile of γ-phenyl-γ-cyanopimelic acid (*XXIV*) (m.p. 68–69°C) (ref.[22]) and 75 ml concentrated hydrochloric acid was heated for 3 h to 100°C. The clear solution formed at first thickened to a crystalline sirup which was cooled and filtered: 12·5 g (96%), m.p. 167 to 169°C (water). For $C_{14}H_{15}NO_4$ (261·3) calculated: 64·36% C, 5·78% H, 5·36% N; found: 64·40% C, 5·78% H, 5·45% N.

The procedure described here is much more suitable than the one from the literature[23] based on alkaline hydrolysis which produces optimally a 50% yield; the reported m.p. was 168–170°C.

4-Cyano-4-(2-carboxyethyl)-1-tetralone (*XXVI*)

A mixture of 10·0 g acid *XXV*, 20 ml thionyl chloride and 0·5 g zinc chloride was refluxed for 2 h in a 50–60°C bath. The excess thionyl chloride was evaporated at reduced pressure. The residue (crude acid chloride) was dissolved in 50 ml 1,1,2,2-tetrachloroethane, 20 g powdery aluminium chloride was added and the mixture was heated under stirring for 5 h to 50–60°C. After two days of standing at room temperature it was decomposed with ice and the precipitated solid (6·6 g, m.p. 180–190°C) was filtered. The product was then purified by precipitation from a 10% solution of potassium hydroxide by acidification, further by crystallization from ethanol and sublimation from a bath at 200–220°C at 0·5 Torr. The product thus obtained melted at 198 to

200°C and was identical with the product m.p. (200°C) prepared by cyclization of the free acid *XXV* with the aid of sulfuric acid[23]. For $C_{14}H_{13}NO_3$ (243·3) calculated: 69·12% C, 5·39% H, 5·76% N; found: 69·64% C, 5·38% H, 5·71% N. The same product was obtained in a low yield by cyclization of acid *XXV* with the aid of polyphosphoric acid at 160°C. For the purification of the crude product vacuum sublimation was used: m.p. 199—200°C (benzene).

3-(1-Cyano-1-tetralyl)propionic Acid (*XXVII*)

Solution of 9·0 g ketone *XXVI* prepared in 200 ml warm acetic acid was carefully cooled and palladium catalyst (from 0·5 g palladium chloride and 3·0 g active charcoal) and 0·5 ml perchloric acid were added. The mixture was hydrogenated in the conventional way on a shaker. After 2·5 h, hydrogen consumption ceased, having almost reached the theoretical value. The mixture was filtered, the filtrate was evaporated at reduced pressure and the residue purified by crystallization from 90% ethanol: 7·80 g (92%), m.p. 173—174°C. For $C_{14}H_{15}NO_2$ (229·3) calculated: 73·34% C, 6·59% H, 6·11% N; found: 73·55% C, 6·63% H, 5·99% N.

α-Phenyladiponitrile (*XXVIII*)

A solution of 6·5 phenylacetonitrile in 30 ml benzene was refluxed for 30 min with 2·2 g sodium amide. After cooling, a solution of 5·2 g 4-chlorobutyronitrile (b.p. 75—76°C/10 Torr, n_D^{20} 1·4468) (ref.[24]) in 20 ml benzene was added dropwise and the mixture was refluxed for 4 h. After cooling, it was decomposed with ice and water, the mixture was extracted with further benzene, the extract was dried and distilled. A total of 7·2 g desired compound boiling at 134 to 136°C/0·4 Torr was obtained. For $C_{12}H_{12}N_2$ (184·2) calculated: 78·22% C, 6·57% H, 15·21% N; found: 78·24% C, 6·80% H, 15·24% N.

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REFERENCES

1. Stach K., Pöldinger W.: Fortschr. Arzneimittel-Forsch. (E. Jucker, Ed.) *9*, 129 (1965).
2. Møller-Nielsen I., Nymark M., Hougs W., Pedersen V.: Arzneimittel-Forsch. *16*, 135 (1966).
3. Bente D., Engelmeier M. P., Heinrich K., Hippius H., Schmitt W.: Arzneimittel-Forsch. *16*, 319 (1966).
4. Jahn U., Haeusler G.: Wien. Klin. Wochschr. *78* (*2*), 21 (1966); Chem. Abstr. *64*, 11 737 (1966).
5. Taen S., Pöldinger W.: Schweiz. Med. Wochschr. *96*, 1616 (1966).
6. Zincke T., Tropp W.: Ann. Chem. *362*, 242 (1908).
7. Criegee R., Höger E., Huber G., Kruck P., Marktscheffel F., Schellenberger H.: Ann. Chem. *599*, 81 (1956).
8. Rouzaud J., Cauquil G., Boyer J.: Bull. Soc. Chim. France *1967* (*2*), 583.
9. Protiva M., Rajšner M., Adlerová E., Seidlová V., Vejdělek Z. J.: This Journal *29*, 2161 (1964).
10. Bradsher C. K., Amore S. T.: J. Am. Chem. Soc. *66*, 1280 (1944).

11. Rimmer R. W., Christiansen R. G., Brown R. K., Sandin R. B.: J. Am. Chem. Soc. *72*, 2298 (1950).
12. Hall D. M., Ladbury J. E., Lesslie M. S., Turner E. E.: J. Chem. Soc. *1956*, 3475.
13. Shriner R. L., Geipel L.: J. Am. Chem. Soc. *79*, 227 (1957).
14. Bosch A., Brown R. K.: Can. J. Chem. *46*, 715 (1968).
15. Mustafa A., Hilmy M. K.: J. Chem. Soc. *1952*, 1434.
16. Eberson L., Petrovich J. P., Baird R., Dyckes D., Winstein S.: J. Am. Chem. Soc. *87*, 3504 (1965).
17. Eberson L., Winstein S.: J. Am. Chem. Soc. *87*, 3506 (1965).
18. Haworth R. D., Sheldrick G.: J. Chem. Soc. *1934*, 864; Chem. Zentr. *1934* II, 1457.
19. Robinson R., Rydon H. N.: J. Chem. Soc. *1939*, 1394; Chem. Zentr. *1940* I, 556.
20. Johnson W. S., Graber R. P.: J. Am. Chem. Soc. *72*, 925 (1950).
21. Cornforth J. W., Robinson R.: J. Chem. Soc. *1949*, 1855.
22. Bruson H. A., Riener T. W.: J. Am. Chem. Soc. *65*, 23 (1943).
23. Hey D. H., Nagdy K. A.: J. Chem. Soc. *1954*, 1204.
24. Allen C. F. H.: Organic Syntheses, Coll. Vol. *1*, 156 (1946).
25. Kulp S. S., Fish V. B., Easton N. R.: Can. J. Chem. *43*, 2512 (1965); Chem. Abstr. *63*, 11393 (1965).
26. Lange J., Makosza M.: Roczniki Chem. *41*, 1303 (1967).
27. Lange J., Makosza M., Urbanski T.: Pol. Pat. 53 334; Chem. Abstr. *70*, 77 373 (1969).

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