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THE MANNICH REACTION OF 9-ACETYL- AND 9,10-DIHYDRO-9-ACETYLANTHRACENE. REDUCTION OF THE MANNICH BASES, AND STEREOCHEMISTRY OF THE 9,10-DIHYDRO COMPOUNDS

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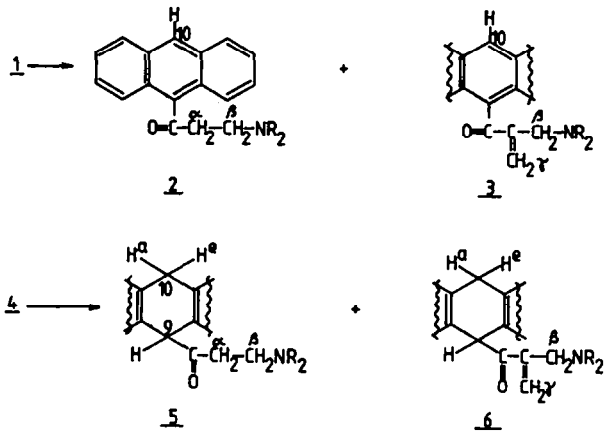
Abstract: The Mannich derivatives (2 and 5) of 9-acetyl-9,10-dihydroanthracene (4) with amines of different sizes were prepared for study of their biological effects. It was found that formation of the normal Mannich product in acetic acid was accompanied by formation of a secondary Mannich product containing a methylidene group (3 and 6). Reduction of compounds 5 with $NaBH_4$ gave aminoalcohols (10), and amino-olefins (11) were prepared from these by elimination. The catalytic reduction of compounds 2 on Pd/C, Raney Ni and Adams catalysts was studied under acidic and basic conditions. In acidic media on Pd/C, the 9,10-dihydro compounds (5) were formed; under basic conditions, on all three catalysts the hydrogenation led to deamination. However, for "steric hindrance" reasons the keto group was not reduced in any of the cases. In compounds 5, the literature data and the H-NMR spectra indicate that the orientation of the 9-substituent is pseudoaxial

In a previous publication[1] we dealt with the biological effect (antibacterial) of Mannich bases of 1-, 2- and 9-acetylanthracene. We have subsequently synthesised a series of such compounds in order to study the structure vs. effect correlations.

Various methods[2-7] are to be found in the literature for the aminoalkyl substitution of anthracenes; of these, we used the Mannich reaction [6,7] to prepare the compounds to be studied. Conditions requiring long heating have been described for the Mannich reaction [6,7]; we modified these conditions slightly and carried out the transformation in glacial acetic acid medium instead of ethanol[9]. This permitted the shortening of the reaction time from 12-20 h to 0.5-2 h. The application of the more forcing conditions, however, led to the appearance of new side-products. It was found that, the Mannich reaction of 9-acetylanthracene (1) and of 9-acetyl-9,10-dihydroanthracene (4) in acetic acid medium gives not only the normal Mannich base (2 and 5) but also a product containing a methylidene group (3 and 6) (see Scheme 1).

Besides the above compounds, at higher temperature a 9-anthryl vinyl ketone, an elimination product, is also formed; this was not studied in detail.

SCHEME 1



R_2N- = dimethylamino (a), piperidino (b), N-methylpiperazino (c), N-trimethylsililmethyl-piperazino (d).

Reactionscheme 1.

The structures of compounds 2, 3, 5 and 6 were identified on the basis of literature descriptions, IR and H-NMR data (Table 1) and elemental analyses.

TABLE 1

Comp.	IR cm^{-1}	ppm ($CDCl_3$ + TMS, or DMSO-$_6$* + TMS)							
		H_α-H_β	H_β	H_r	H_{10}	$H^{e'}$	$H^{a'}$	$J_{H^{e'}H^{a'}}$ Hz	H_9
2_b	1700	3.0 3.7*	-	-	8.10 8.90	-	-	-	-
3_b	1600	-	3.45 4.40*	6.0 5.55 7.0 5.92*	8.10				
5_a	1715	3.0	-	- -	-	3.73	4.18	18	4.95
6_a	1658	-	3.05	6.06 5.55	-	3.70	4.30	18.5	5.08

The data in Table 1 clearly document the structures of the compounds synthesised. However, the orientation of the 9-substituent in compounds 5 and 6 needs more detailed interpretation.

In both compounds (5 and 6), the chemical shift of the C-10 protons and the large geminal coupling constant bear witness to the non-planarity of the meso ring. Dreiding models of the two possible boat forms reveal that the more probable conformation is that in which the 9-acyl group occupies a pseudo-axial (a') position (because of the steric hindrance of the peri hydrogens). In this orientation, the 9-substituent exerts a deshielding effect on $H^{a'}$, and this gives rise to a greater difference in the chemical shifts of the two protons ($H^{a'}$ and $H^{e'}$), than would be expected.

An approach to the conformation can be made from the methylene shift in 9,10-dihydroanthracene, δ3.80, (which is an average value for $H^{a'}$ and $H^{e'}$ and that for the pseudo-equatorial (e') C-10 proton in the "fixed" conformation, δ3.73. These values lead to a predicted shift of δ3.87 for $H^{a'}$. The observed shift of 4.18 ppm is evidence that the 9-substituent must be in the pseudo-axial position (at least this is the dominant population in the equilibrium mixtures); otherwise, there would not have been such a great difference between $H^{a'}$ and $H^{e'}$. This

conclusion is in accordance with the literature finding that the meso ring of 9-alkyl-9,10-dihydroanthracene is more stable in the boat conformation in which the 9-substituent occupies a pseudo-axial position[10].

Experiments were performed at 90 or 120°C in acetic acid. The course of the reaction was followed by thin layer chromatographic control, and the results were evaluated qualitatively. It was found that the optimum conditions for the reaction were heating for 20-40 min at 120°C, and the addition of formaldehyde in several portions. The results indicate that, at a high initial formaldehyde concentration, the Mannich base formed reacts with further formaldehyde to yield 3 and 6. The mechanism of this secondary process is not yet known, but it has been observed that this transformation is catalysed by acetic acid[11]. If the Mannich base is heated with paraformaldehyde in DMF, it is converted to a product of type 3, containing a methylidene group[9].

Studies were made of the catalytic hydrogenation of the resulting Mannich bases with various catalysts under acidic or basic conditions. It is known that the oxo group of 9-acetylanthracene can not be hydrogenated catalytically because of steric hindrance[6]; accordingly, transformation of compound to a side-chain alcohol was not considered.

Table 2 presents results on hydrogenation experiments with compounds 2. The designations of the products are the same as in Scheme 1, together with the further products 1-(9-anthryl-1,2,3,4-tetrahydro)-3-piperidinopropan-1-one (7), 1-(9-anthryl-1,2,3,4-tetrahydro)-propan-1-one (8) and 1-(9-anthryl)-propan-1-one (9). Products for which the percentage yield is not given in the Table were not isolated, but were detected by thin-layer chromatography through the use of comparative substances.

TABLE 2

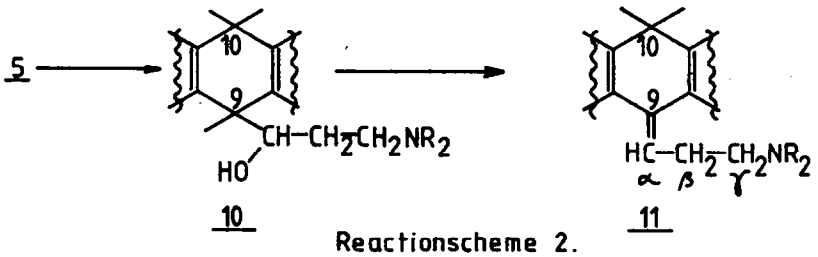
Method	Solvent	t °C	Pressure Pa	Reaction time h	Product %
H_2, Pd/C	glacial acetic acid, HCl, water	25	1.01×10^{-4}	20	5a(62) + 7a + 2a
H_2, Pd/C	"	25	"	6	5a(10) + 2a(70)
H_2, Pd/C	EtOH	25	"	5	9(51) + 8
H_2, Raney Ni	EtOH	25	"	5	9(51) + 8
HI/P[7]	glacial acetic acid	120	"	2.5	5a(25)

On Pd/C under acidic condition, the main product was 5, with a small amount of 7. However, hydrogenation of the hydrochloride of the morpholine derivative 2 on PtO_2 in MeOH resulted mainly in the compound of type 7[6]. The difference in the results is a sign of the different selectivities of the two catalysts.

When the bases of compounds 2 were hydrogenated in EtOH, the C-N bond underwent hydrogenolysis on all three catalysts at atmosphere pressure, 9-propionylanthracene (9) being formed as main product. T.l.c. also revealed 8 in all cases. The difference between catalytic hydrogenations under acidic and basic conditions can be ascribed to the anchor effect[12]; this is connected with the adsorption of the protonated and the non-protonated amine on the surface of the catalyst. A further conclusion from the experiment is that 'steric' hindrance is present, for the oxo group was not reduced in any of the cases under the applied conditions.

The nature of this steric hindrance was examined by investigating the possibilities of catalytic hydrogenation on Pd/C of the oxo group of the dihydro derivative 5 and the olefinic bond of compounds 11. However, experiments in acidic medium to avoid desamination did not lead to saturation of the π-bond in any of the compounds. An idea of the nature of the "steric" hindrance can be conceived if it is considered that the keto groups of the compounds in question become accessible in other chemical reactions. Thus, 9-acetylanthracene can be reduced by the Meerwein-Verley method[13] or with $LiAlH_4$, its dinitro-phenylhydrazone can be prepared[13], and compound 5 too can be reduced with $NaBH_4$ (Scheme 2).

SCHEME 2



Reactionscheme 2.

It may be added that the acyl group in compound 5 is pseudo-axial (see above) and hence rises above the plane of the ring; the acyl group in 9-acetylanthracene is not coplanar either[14]; and a Dreiding model of compound 11 shows that its propylidene group is likewise elevated above the plane of the ring. Accordingly, it appears obvious that the "steric" hindrance is a result of selective bonding. The molecule is bound with the plane of the ring on the surface of the catalyst, while the π-bond is inclined out from this plane and are situated well away from the active surface of the catalyst, so that they can not be hydrogenated.

EXPERIMENTAL

The IR spectra were recorded on a Unicam SP 200, and the H-NMR spectra on a JEOL 60 mHz instrument. Thin-layer chromatography was performed on DC-Alufolien Kieselgel G_{254}, with C_6H_6-$CHCl_3$-MeOH = 10:10:6. The calculated and found elemental analysis data are given in the sequence C, H, N and are expressed as percentages.

General Method of Preparation of Mannich Bases

The components of the reaction are 9-acetylanthracene (1)[15,8], or 9-acetyl-9,10-dihydroanthracene (4)[7], with dimethylamine.HCl (a), piperidine.HCl (b), N-methylpiperazine.HCl (c) or N-trimethylsilylmethylpiperazine.HCl (d) as secondary amine, and paraformaldehyde, in molar ratios of 1:1:1 or 1:1:2. The reaction mixture is heated at 90 or 120°C for 30-110 min in 5-7 mol glacial acetic acid/mol reactant. After cooling, the reaction mixture is poured into ice-water and extracted with ether (unchanged 1 and 4 recovered from the ether solution by evaporation). Under ice-water cooling, the aqueous phase is neutralised with 10% Na_2CO_3, then made slightly alkaline, and extracted with ether. The ether solution is washed three times with water, and then dried over anhydrous Na_2CO_3. The ether is distilled off. The resulting crude product contains the Mannich base, together with various amounts of 3 or 6 as impurity, depending on the conditions applied. The crude product is dissolved in EtOH and converted to the hydrochloride by acidification to pH 5 with 15% HCl/EtOH. Ether is added until opalescene. Crystallisation generally begins after some minutes. As necessary, the material is put into a refrigerator and recrystallised from an EtOH/ether mixture. The overall yields are 40-70% (Table 3).

General Description of catalytic hydrogenation of the Mannich Compounds 2 and 5

The hydrochlorides of Mannich compounds are hydrogenated on 10% Pd/C in a 10-fold amount of 90% glacial acetic acid, while the free base is hydrogenated in the presence of Pd/C, Raney Ni or PtO_2 in a 10-fold amount of EtOH, for 8-20 h at atmospheric pressure. The quantity of catalyst is 5% of that of the Mannich compounds. Working-up of the reaction mixtures was performed in the usual manner.

Catalytic Hydrogenation of 2b

Under acidic conditions:

From 3.4 g (11 mmol) 2b, in the presence of 0.4 g Pd/C, in solution of 30 ml 90% glacial acid and 2 ml conc. HCl, for 24 h: 2.4 g (75.11%) crude product. Chromatography reveals starting material, 5b and a little 7b. Conversion to hydrochloride and recrystallisation from EtOH/ether yields 1.9 g (60%). M.p. 200-201°C. The IR and H-NMR data fully conform with those of 1-(9,10-dihydro-9-anthryl)-3-piperidinopropan-1-one.HCl, (5b) prepared by Mannich reaction (8b). On hydrogenation for 6 h, only 10% of the substance is converted.

Under basic conditions:

On all three catalysts in EtOH medium, the base 2b gives 9-propionylanthracene: yields 50.38% on Pd/C, 51% on Raney Ni, and 46% on PtO_2, the remaining material being unchanged starting compound and other, not isolated products. M.p. 57-58°C. Literature[16] m.p. 55-57°C. IR: 1700 cm^{-1}. H-NMR: δ8.5 (H_{10}), δ3.0 (Hβ, quartet, 2 protons), δ1.47 (Hα triplet, 3 protons).

TABLE 3

Comp.	Formula	Calc/Found % C	H	N	Mp °C	H-NMR values in δ ppm H_α,H_β	H_β	H_γ	H_{10}	$H^{e'}$	$H^{a'}$	H_9	IR cm^{-1}
		72.72	6.42	4.46		3.70	"	"	8.9	"			1705
2a	$C_{19}H_{20}ClNO^c$	73.10	6.37	4.67	170-71[a]	2.82							
2b	$C_{22}H_{23}N^c$	83.24 83.10	7.30 7.40	4.41 4.48	84-86[b] 190-91[a]	3.0[M]	"	"	8.4	"	"	"	1702
3a	$C_{20}H_{20}ClNO^d$	72.72 73.40	6.19 6.60	4.30 4.60	221-22[a]	"	3.45	6.0 5.55	8.75	"	"	"	1660
2C+ 3C	1:1 mixture[c]	"	"	"	195-199[a]	"	"	"	"	"	"	" 1660	1702
5d	$C_{25}H_{36}Cl_2N_2OSi^c$	62.61 62.31	7.56 7.72	5.84 5.90	180-83[a]	"	"	"	"	4.20	3.70	4.85	1715
5B	$C_{22}H_{26}ClNO^c$	74.24 74.12	7.36 7.30	3.93 3.97	201-2[a]	"	"	"	"	4.35	3.85	5.12	1712
6b	$C_{23}H_{25}NO^d$	83.84 83.50	7.60 7.49	4.23 4.13	133-34[b]	6.0 5.55	"	"	"	4.30	3.70	5.80	1658
5a	$C_{19}H_{22}ClNO^c$	72.25 72.40	7.02 6.87	4.44 4.62	182-83[a]	"	"	"	"	4.20	3.80	4.80	1713
6a	$C_{20}H_{21}NO^d$	82.44 82.51	7.26 7.38	4.81 4.64	93.5[b]	6.34 5.73	"	"	"	4.40	3.80	5.90	1662

Remarks: a: hydrochloride, b: base c: heated at 120°C for 30 minutes in 1:1:1 molar ratio, d: heated at 120°C for 90 minutes in 1:1:2 molar ratio, M: multiplet

Catalytic Reduction of 5a

Under acidic conditions, 2.0 g 5a. HCl is hydrogenated for 20 h on 0.5 g Pd/C in 20 ml 90% glacial acetic acid. Only the hydrogen taken up by the catalyst is consumed. After processing, 1.9 g of the hydrochloride starting material is recovered. M.p. 181-182°C.

$NaBH_4$ Reduction of Aminoketones (5) to Aminoalcohol (10) and Elimination of the Aminoalcohol to give the Olefin (11) 1-(9,10-Dihydro-9-anthryl)-3-dimethylaminopropan-1-ol.HCl (10a)

2.2 g (7.0 mmol) aminoketone 5a in 20 ml MeOH is reduced with 1.0 g $NaBH_4$ as usual. Yield: 1.2 g (54.04%) hydrochloride. M.p. 212-213°C. Calcd.: ($C_{19}H_{24}ClNO$) 71.79, 7.61, 4.41; found: 71.63, 7.52, 4.63, IR: 3350 cm^{-1} (associated OH).

Elimination: 2.0 g (6.3 mmol) 10a in 15 ml abs. $CHCl_3$ is refluxed for 8 h with 1.19 g (10.0 mmol) $SOCl_2$. The solvent is distilled off, the residue is dissolved in EtOH, and the solution is clarified with bone charcoal. Crystallisation occurs on the addition of ether. 1.1 g (55.26%) 3-(9,10-dihydro-9-anthryl)-1-dimethylaminoprop-3-ene. HCl is obtained. M.p. 228.5-230°C. Calcd.: ($C_{19}H_{22}ClN$) 76.11, 7.40, 4.67; found: 76.50, 7.50, 4.65. H-NMR (for assignments see formula 11): δ3.28, 3.32 (H_β, H_γ, 4 protons), δ3.58 (H^a, H^e multiplet, 2 protons), δ7.18 (Hα olefinic proton).

1-(9,10-Dihydro-9-anthryl)-3-piperidinopropan-1-ol (10b)

Prepared from 7.0 g (19.0 mmol) aminoketones 5b in 50 ml MeOH with 1.7 g $NaBH_4$. Yield: 5.2 g (82.11%). R_f of the viscous oil: 0.38. This material is used in the subsequent reaction. Calcd.: ($C_{22}H_{27}NO$) 82.20, 8.41, 4.36; found; 82.40, 8.20, 8.20, 4.52 IR), 3350 cm^{-1} (associated OH).

Elimination 3.4 g (10.0 mmol) 10b is heated in 20 ml abs. $CHCl_3$ with 1.78 g (15 mmol) $SOCl_2$ for 8 h. 1.2 g (34.3%) 3-(9,10-dihydro-9-anthryl)-1-piperidinoprop-3-ene. HCl (11b) is obtained. M.p. 213-215°C. Calcd.: ($C_{22}H_{26}ClN$) 77.74, 7.71, 4.12; found: 77.65, 7.75, 4.26, H-NMR: δ3.6 (H^a H^e multiplet), δ7.18 (Hα, olefinic proton).

1-(9,10-Dihydro-9-anthryl)-3-(N-trimethylsilylmethylpiperazino)-propan-1-ol. 2HCl (10d)

Prepared from 3.0 g (6.25 mmol) aminoketone.2HCl 5d in 40 ml MeOH with 0.23 g (6.25 mmol) $NaBH_4$. 2.0 g (67%) 10d is obtained. M.p. 200-204°C. Calcd.: ($C_{25}H_{38}Cl_2N_2OSi$) 62.35, 7.95, 5.82; found: 62.85, 8.12, 5.63, IR: 3400 cm^{-1} (associated OH), 860 cm^{-1} (Si-C bond).

Elimination: 1.8 g (3.7 mmol) 10d in 10 ml abs. $CHCl_3$ is heated with 0.66 g (5.5 mmol) $SOCl_2$ for 8 h. 1.1 g (83.58%) 3-(9,10-dihydro-9-anthryl)-1-(N-trimethylsilylmethylpiperazino)-prop-3-ene.2HCl (11d) is obtained. Calcd.: ($C_{25}H_{36}Cl_2N_2Si$) 64.77, 7.83, 6.04; found: 64.45, 7.90, 6.35. H-NMR: 0.3 (CH_3-Si), δ3.27, δ3.40 (H 4 protons) δ3.6 (H^a H^e multiplet, 2 protons), δ7.15 (Hα, olefinic proton).

Catalytic Hydrogenation of the Amino-olefin.HCl (11b)

When hydrogenated at atmospheric pressure for 10 h on 0.5 g Pd/C in 15 ml glacial acetic acid, 1.0 g 11b.HCl does not take up hydrogen. Isolation yields the unchanged starting material. M.p. 215°C. The H-NMR and elemental analysis conform with the data for the starting material.

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