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OXIDATION OF TERTIARY POLYCYCLIC AMINES BY RuO_4[1]

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Abstract - The reactions of certain tertiary polycyclic amines such as N-benzyl-9-azabicyclo-[3,3,1]-nonane, N-benzyl-5,6-dihydro-11H-dibenz[b,e]azepine, and N-benzyl-1,2,3,4-tetrahydroisoquinoline with ruthenium tetroxide, taking place in both heterogeneous and homogeneous systems, have made it possible to establish the order of reactivity of the various methylene groups adjacent to the nitrogen with respect to this oxidizing agent.

Ruthenium tetroxide is an effective oxidizing agent for many organic compounds[2]. It can be used in heterogeneous systems consisting of water and halogenated solvents, when it is generated "in situ" by the oxidation of ruthenium dioxide hydrate with sodium periodate or some other vigorous oxidizing agent. Alternatively, it can be used in homogeneous systems by adding its solution in a halogenated solvent to a solution, also in a halogenated solvent, of the compound to be oxidized.

The sparse and conflicting data in the literature[3] relating to the oxidation of nitrogen-bearing compounds by ruthenium tetroxide have motivated us in the past to look more closely at this reaction, with a view to achieving a selective oxidation of the carbons adjacent to the nitrogen atom.

To define the reactivity of such carbon atoms, we oxidized various substrates derived from pyrrolidine, piperidine[4], and morpholine[5], with alkyl- or acyl-substituted nitrogen atoms.

The low reactivity of the benzyl methylene group in the N-benzyl derivatives of pyrrolidine and piperidine substituted in position 3, and the consequent production of the corresponding N-benzylimides, enabled us to propose[6] the RuO_4 oxidation as a valid alternative to Von Braun's reaction for the degradation of amides.

The low reactivity of the benzyl methylene group has also been demonstrated[7] in piperidine derivatives, either unsubstituted, or substituted in position 2, and contrasts with the results obtained by oxidizing N-benzylmorpholines[7] and N-acylbenzylamines[8].

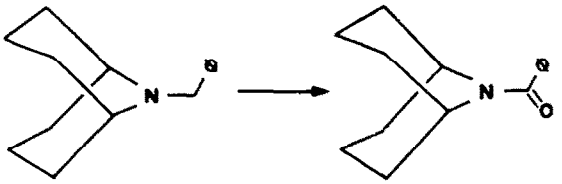
The present work is a contribution towards the verification of the reactivity of cycloaliphatic and benzyl methylene groups bound to a nitrogen atom, both when they are in positions such that their conformational mobility is influenced by it and when they are present in variable numbers, so that a reactivity sequence can be established for them.

The oxidations were sometimes carried out in a heterogeneous system for various times, in an attempt to isolate any intermediates that might appear, and sometimes in a homogeneous system so as to be able to control not only the temperature and the reaction time, but also the amount of the reagent used. Another reason for using the two oxidation systems was to enable us to establish the influence of the medium on the reaction yields.

The first substrate we examined was N-benzyl-9-azabicyclo-[3,3,1]-nonane 1a, synthesized by the method of Dupeyre and Rassat[9], in which the only position liable to be oxidized should be the benzyl methylene.

This choice was due to the fact that simpler models such as the 2-methyl or α,α'-dimethyl benzyl derivatives of pyrrolidine or piperidine cannot be used, since it has been observed[10] that methyl carbons adjacent to the nitrogen are fairly easily oxidized to carbonyl groups.

The oxidation of 1a (Fig.1) in a homogeneous system with an equimolar quantity of ruthenium tetroxide dissolved in carbon tetrachloride, over a period of 1h at ambient temperature, gave as the only product N-benzoyl-9-azabicyclo-[3,3,1]-nonane 2a, in a yield of 65%.



1a 2a

Fig. 1

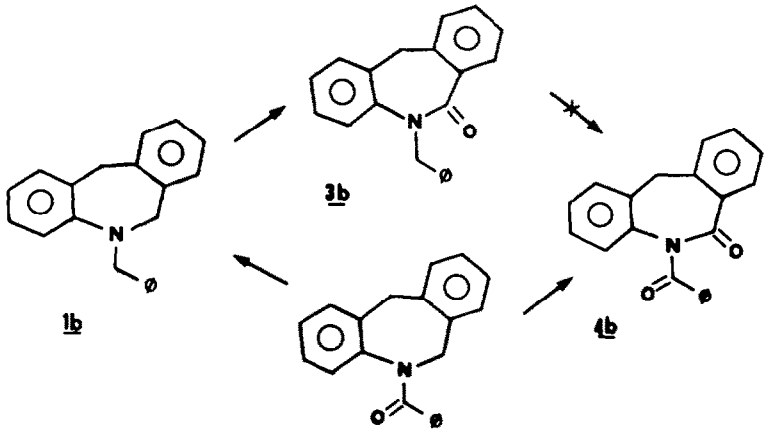
This result demonstrates that a benzyl methylene group bound to a piperidine nitrogen can only be oxidized selectively after the ring carbon adjacent to the nitrogen have been blocked by some means, e.g.by being inserted in the head of a bridge.

Having established that cycloaliphatic methylene groups can be oxidized more easily than exocyclic benzyl methylenes, it became interesting to see what would happen when the same molecule included two benzyl groups, an endocyclic and an exocyclic one, as in the case of N-benzyl-5,6-dihydro-11H-dibenz[b,e]azepine 1b, obtained by reducing the corresponding benzoyl derivative 2b with lithium tetrahydroaluminate. The oxidation of 1b (Fig.2) in a heterogeneous system for 8h at ambient temperature produced only the N-benzyl-6-oxo derivative 3b, with a yield of 49%. The same reaction carried out in a homogeneous system for 1h at ambient temperature again gave 3b, but now in a yield of 80%.

When the benzoyl derivative 2b was oxidized for 48h at ambient temperature and in a hetero geneous system, we obtained, in addition to 37% of the initial product, a 41% yield of the N-benzoil-6-oxo derivative 4b. Subsequent oxidation of 3b in a homogeneous system at ambient temperature allowed the initial product to be recovered completely.

The low reactivity observed in the last two oxidations confirms what has already been found[3d,4], namely that the reactivity of nitrogen-bearing compounds in oxidations with ruthenium tetroxide seems to be associated with the availability of the nitrogen's pair of electrons. Thus, in both of the cases mentioned above the electron pair of the nitrogen, apart from being conjugated with the aromatic ring, participates in conjugation with the carbonyl group. This reduces its availability and hence the reactivity. In particular, since the amide bond in 3b is inserted in a ring, the delocalization of the electron pair is more pronounced, and this leads to a total absence of reactivity, at least over reaction times considered in this work.

Having noted previously[4a] that endocyclic methylene groups with limited conformational freedom can be oxidized more easily than exocyclic methylene groups, it may be thought that the low reactivity observed with 3b could also be due to the fact that the final oxidation must occur at an exocyclic methylene group, in contrast to what happens in 2b, where it is the endocyclic benzyl methylene that is oxidized.



1b 3b 4b 2b

Fig. 2

The last of the compounds we examined was N-benzyl-1,2,3,4-tetrahydroisoquinoline 1c, obtained by benzylation of 1,2,3,4-tetrahydroisoquinoline, in which apart from the two (endocyclic and exocyclic) benzyl groups there is an additional cycloaliphatic methylene group adjacent to the nitrogen atom.

Oxidation of 1c (Fig.3) in a heterogeneous system for 26h at ambient temperature gave the N-benzoyl-1,3-dioxo derivative 4c in a yield of 39%.

In contrast to what has been observed in the past concerning the impossibility of fully oxidizing the cyclic N-benzylimides[6], this represents the first case in which all three methylenes adjacent to a nitrogen undergo oxidation.

amount of ruthenium tetroxide in carbon tetrachloride, the only reaction product obtained was 2c, with a yield of 68%.

To determine which of the two methylene groups remaining in 2c would be oxidized first, and also in the attempt to isolate any di-oxidation products, we first oxidized 2c in a heterogeneous system for 9h at ambient temperature, obtaining 4c in a yield of 46%. We then reoxidized 1c in a homogeneous system with twice the stoichiometric quantity of ruthenium tetroxide for 2h at ambient temperature, and obtained a product mixture which, when analysed by gas chromatography, was found to consist of 2c (58% yield) and 4c (13% yield). In neither case could we demonstrate the presence of any di-oxidation products.

In view of the failure of these attempts, we

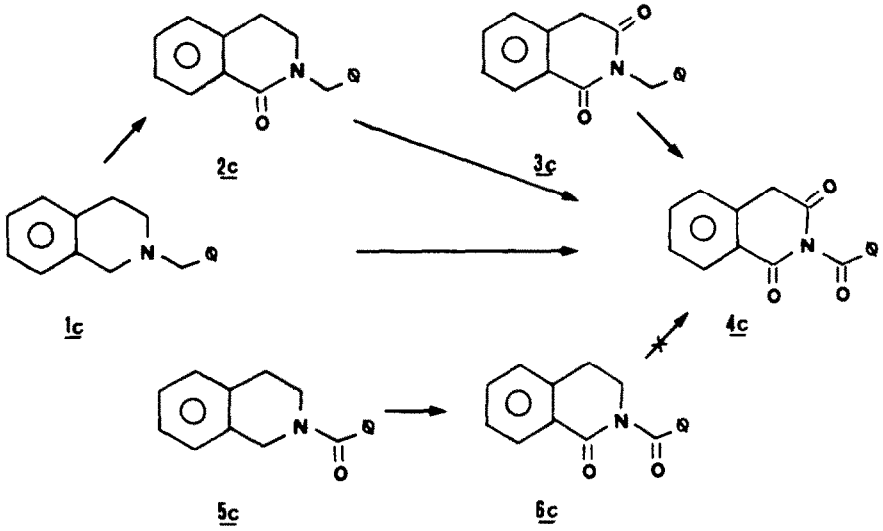


Fig. 3

To establish the course of the reaction from 1c to 4c, and to attempt to isolate the intermediates, we repeated the above reaction under controlled conditions: oxidation of 1c in a heterogeneous system for 2h at 0°C gave the N-benzyl-1-oxo derivative 2c in a yield of 48%. When 1c was again oxidized, but in a homogeneous system, for 1h at - 10°C with a stoichiometric

tried to establish the second stage of oxidation by another route, namely by oxidizing N-benzoyl-1,2,3,4-tetrahydroisoquinoline 5c. The oxidation of 5c, carried out in a heterogeneous system for 23h at ambient temperature, gave only the N-benzoyl-1-oxo derivative 6c in a yield of 69%, without any evidence of the formation of 4c.

Our failure to oxidize 6c completely to 4c shows

that in the oxidation of the amine 1c, if the process takes place in successive stages, then after the endocyclic benzyl methylene in position ' the second methylene to be oxidized should be the cycloaliphatic one in position 3, leading to the formation of the N-benzyl-1, 3-dioxo derivative 3c, which would show an unexpectedly high reactivity.

In fact, the oxidation of 3c, prepared by the method described by Pulvermacher[11], in a homogeneous system for 2h, gave 4c in a yield of 87%. The high reactivity of 3c compared to both the pyrrolidine and the piperidine N-benzylimides, and to the compound 6c, may be due to the fact that the introduction of an extensively conjugated system into the piperidine part of the molecule flattens the ring itself, with a consequent increase in the ring strain that, by reducing the effectivness of the conjugation, enhances the availability of the nitrogen's pair of electrons.

The experimental data reported in this work enabled us to obtain a clearer picture of the reactivity of benzyl methylene groups, and more generally, to define a scale of reactivities for methylene groups adjacent to a nitrogen atom. It can be deduced that exocyclic methylene groups are less reactive than endocyclic ones, and that of the latter, the benzyl-type methylenes are more easily oxidized than the others.

Finally, as for the reaction yields, we observed that in general the reactions carried out in homogenous systems give higher yields than the oxidations carried out in heterogeneous systems, and this suggests that the lower yields in the second case may be due in part to hydrolysis of the oxidation products.

EXPERIMENTAL

The elementary analyses were carried out by Dr. A. Reho of the Institute of Pharmaceutical Chemistry, Bari, on a Hewlett-Packard Mod. 185 C,H,N analyser. The melting points were determined using a Buchi-Tottoli instrument, and are uncorrected.

The IR, UV, NMR and MASS spectra were determined respectively with a Perkin-Elmer 283 spectrophotometer, a Cary 15 spectrophotometer (in CH_3OH, 1-cm cell), a Varian HA 100 spectrometer (in $CDCl_3$ unless otherwise indicated, with TMS as internal standard; chemical shifts were expressed in δ units), and a Hewlett-Packard GC-MS 5990A spectrometer operating at 70eV, connected to a Hewlett-Packard 9825A computer. The gas-chromatographic determination were carried out in a Hewlett-Packard 5840A instrument fitted with a flame-ionization detector.

General procedure for oxidations in a heterogeneous system

A solution of the amine to be oxidized (0.01 mole) in CCl_4 (10 ml) was added to a mixture of CCl_4 (100 ml) and H_2O (100 ml) containing $NaIO_4$ (10 g) and $RuO_2 \cdot xH_2O$ in catalytic amount (0.1g), and the mixture was shaken vigorously. The reaction was followed with TLC or GC, and interrupted when the initial product had disappeared. 5 ml of IspOH was added to the reaction mixture, the phases were separated, the organic phase was dried over anhydrous Na_2SO_4, and the solvent was driven off under reduced pressure. The reaction residue was suitably purified.

General procedure for oxidations in a homogeneous system

A solution of a stoichiometric quantity of RuO_4 in CCl_4, prepared by Nakata's method[12] and standardized according Nowogrocki and Tridot[13], was added drop by drop to a solution of the amine to be oxidized (0.01 mole) in alcohol-free CCl_4 (100 ml). The reaction was followed by TLC or GC and was interrupted when the starting product had disappeared. 5 ml of IspOH was added, the precipitated ruthenium dioxide was filtered off, and the resultant solution was evaporated under reduced pressure. The reaction residue was suitably purified.

Purification of halogenated solvents for oxidation in homogeneous system

The desired amount of CCl_4, or CH_2Cl_2 was shaken with a 10% solution of $NaIO_4$ in the presence of 0.01 g of $RuO_2 \cdot xH_2O$ until a persistent yellow colour was established in the organic phase. The

phases were separated and the yellow organic phase was extracted with 4N NaOH until colorless, washed with water until neutral, and then distilled 3 times over P_2O_5 in a current of N_2.

N-Benzyl-5,6-dihydro-11H-dibenz[b,e]azepine 1b

2b (2g) was refluxed in anhydr. THF (50ml) with $LiAlH_4$ (0.75g) for 8h and left to stand overnight, with stirring at room temperature. The excess hydride was destroyed with water, the phases were separated, the organic phase was dried over anhydr. Na_2SO_4, and the solvent was driven off under reduced pressure. The residue was subjected to chromatography on SiO_2 column (eluent: benzene), and gave a liquid fraction consisting of 1b (1g, yield 52%), which was then purified by distillation under reduced pressure [lit.[15]: b.p. 180-190°C (0.12mmHg)]; ^{1}H-NMR: 4.20 (s, 2H, benzyl), 4.28 (s, 2H, benzyl), 4.33 (s, 2H, benzyl), 6.30-7.50 (m, 13H, ArH); [Found(%): C 88.17 H 6.62, N 4.84. Calcd. for $C_{21}H_{19}N$: C 88.38, H 6.71, N 4.91].

N-Benzoyl-5,6-dihydro-11H-dibenz[b,e]azepine 2b

5,6-dihydro-11H-dibenz[b,e]azepine (5g) was refluxed in CH_2Cl_2 for 14h with an equimolecular quantity of benzoyl chloride and triethylamine. After cooling, the reaction mixture was washed with 2N HCl, water, saturated solution of $NaHCO_3$ and then again water. After drying over anhydr. Na_2SO_4, the solvent was driven off under reduced pressure to produce a solid residue that, on crystallization, gave 2b (4.14g, yield 54%): m.p. 127°C(acetone); ^{1}H-NMR: 4.17 (broad, 2H, C-11 H), 5.20 (broad, 2H, C-6 H), 6.60-7.50 (m, 13H, ArH); IR(KBr): 1643cm^{-1} (νC=O); [Found(%): C 84.06, H 5.61, N 4.61. Calcd. for $C_{21}H_{17}NO$: C 84.25, H 5.72, N 4.68].

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TABLE 1. Oxidation of tertiary polycyclic amines by ruthenium tetroxide[a].

Starting material	Oxidation conditions system	time(h)	temp.(°C)	Reaction product	Yield(%)	M.p.(°C)
1a	homog.	1	20	2a	65	107-108 ($CHCl_3$/hexane) [lit.[14]]
1b	heter.	8	"	3b	49	148-150 (ethanol) [lit.[15, 16]]
1b	homog.	1	"	3b	80	
2b	heter.	48	"	4b	41[b]	150 (acetone)
1c[17]	"	26	"	4c	39	183-184 ($CHCl_3$/hexane)
1c	"	2	0	2c	48	oil
1c	homog.	1	-10	2c	68	
1c	"[c]	2	20	2c, 4c	58; 13[d]	
2c	heter.	9	"	4c	46	
3c[11]	homog.	2	"	4c	87	
5c[18]	heter.	23	"	6c	69	130-131 ($CHCl_3$/hexane) [lit.[18]]

[a]The elemental analyses show a deviation of ±0.3% from the calcd. values; [b]it has been recovered 37% of 2b; [c]with twice the stoichiometric amount of RuO_4; [d]analysed by gas-cromatography [Column packed with 2% OV-101 + 0.2% Carbowax on Chromosorb WHP 100-120 mesh; column length 2 m; N_2 flow rate 36.8 ml/min; column temp. constant 170°C; ret. time: 10.67 min (2c), 19.88 min (4c)].

TABLE 2. Spectral data.

Compound	I.R. $\nu(cm^{-1})$	N.M.R.	MASS m/e(%)
1a	-	-	M^+ 215(67), 173(45), 172 (100), 91(83), 65(15), 39(10).
2a	(KBr) 1620 $\nu_{C=O}$	1.50-2.50(m, 12H, aliph. H), 3.93(broad, 1H, C-1 or C-5 H), 4.97(broad, 1H, C-5 or C-1 H), 7.50(s, 5H, ArH).	M^+ 229(79), 105(100), 77 (48), 51(11).
3b[16]	(KBr) 1625 $\nu_{C=O}$	3.725(A'B', 2H, ν_B, 341Hz, ν_A, 404Hz, $J_{A'B'}$, 13Hz, C-11 H), 5.295(AB, 2H, ν_B, 512Hz, ν_A 547Hz, J_{AB} 15Hz, $-CH_2-\phi$), 6.70-7.60(m, 12H, ArH), 7.70-7.90(m, 1H, ArH).	-
4b[a]	(KBr) 1700, 1655 1630 $\nu_{C=O}$	5.22(s, 2H, C-11 H), 6.40-8.50(m, 13H, ArH).	-
2c	(film)1645 $\nu_{C=O}$	2.87(t, 2H, J 7Hz, C-4 H), 3.43(t, 2H, J 7Hz, C-3 H), 4.75(s, 2H, $-CH_2-\phi$), 7.00-7.50(m, 8H, ArH), 8.00-8.20(m, 1H, ArH).	M^+ 237(88), 91(100), 65 (45), 39(19).
3c	(KBr) 1705, 1660 $\nu_{C=O}$	4.10(s, 2H, C-4 H), 5.21(s, 2H, $-CH_2-\phi$), 7.00-7.80(m, 8H, ArH), 8.10-8.40(m, 1H, ArH).	M^+ 251(100), 223(30), 222 (28), 132(26), 118(67), 119(52), 91(51), 77(11).
4c[b]	(KBr) 1723, 1708 1679 $\nu_{C=O}$	5.20(s, 2H, C-4 H), 7.10-8.60(m, 9H, ArH)	M^+ 265(40), 104(100), 76 (78), 50(40).
6c	(KBr) 1670 $\nu_{C=O}$	3.12(t, 2H, J 6Hz, C-4 H), 4.08(t, 2H, J 6Hz, C-3 H, 7.10-7.70(m, 8H, ArH), 7.90-8.20(m, 1H, ArH).	M^+ 251(35), 105(100), 77 (60), 51(13).

[a]U.V.(c= $6.07 \cdot 10^{-5}$ mole/ml): λ_{max} 327 nm (log ε 3.48), 271 nm (log ε 4.25).

[b]U.V.(c= $8.07 \cdot 10^{-5}$ mole/ml): λ_{max} 250 nm (log ε 3.73), 230 nm (step, log ε 3.92).