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The Jacobson Reaction of *N*-Nitroso-6,9-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one and the Nitrosation of Benzolactams

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The nitrosation of 6,9-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (*3a*) and 5,8-dimethylhydroisocarbostyril (*2*) occurs in both cases on the nitrogen atom. 5,8-Dimethylhydrocarbostyril (*3b*) and hydrocarbostyril (*3c*) nitrosate both on the nitrogen atom and on the aromatic ring. In deuterochloroform *3b* gives *C*-nitrosation and in trifluoroacetic acid-trifluoroacetic anhydride both *C* and *N*-nitrosation. In trifluoroacetic acid-trifluoroacetic anhydride *3c* seems to substitute two nitroso groups on the aromatic ring. In dry benzene (*5a*) rearranges to give 6-methyl-7-(γ-carboxypropyl)-1H-indazole (*8*). The *trans*-diazoester (*7a*) may be an intermediate in the Jacobson reaction.

The relative ease of rearrangement of *N*-nitrosobenzolactams (*5*) (Scheme 1) to *trans*-diazoesters (*7*) has been our concern as well as Huisgen's.[1] However, Huisgen found as we did in this study that the preparation of *N*-nitroso derivatives of six-membered benzolactams was difficult. By placing a methyl group *peri* to the *N*-nitroso group of the benzolactam, some insight into the mechanism of the Jacobson reaction [2] (the conversion of *o*-methyl-*N*-nitroso-*N*-acylarylamides to indazoles) might be gained. We conclude that the *trans*-diazoester (*7a*) may be an intermediate of the Jacobson reaction.

We base our conclusions on the fact that only the seven-membered ring system gives both the coupling observed by Huisgen and an indazole observed by us, whereas the six-membered ring system gives neither coupling nor an indazole as we shall show presently. However, our six-membered ring system studies are complicated by the instability of the *N*-nitroso compounds.

Nitrosation of the seven-membered ring of 6,9-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (*3a*) gave (as also observed by Huisgen [1])

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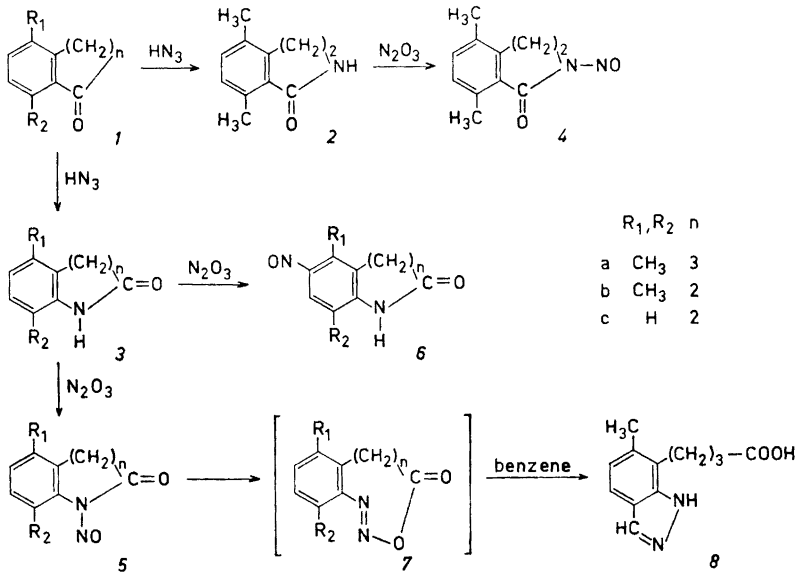

Scheme 1

N-nitroso-6,9-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (*5a*). Evidence for the rearrangement of *5a* to the *trans*-diazoester (*7a*) was presented by Huisgen when he was able to couple it with β-naphthol. We rearranged *5a* in dry benzene to 6-methyl-7-(γ-carboxypropyl)-1H-indazole (*8*). The *trans*-diazoester (*7a*) is a logical intermediate for the latter reaction.

Nitrosation of 5,8-dimethylhydrocarbostyril (*3b*) with nitrous anhydride in acetic acid-acetic anhydride gave a yellow solid characteristic of *N*-nitroso compounds when the solution was poured into water. However, this yellow solid turned white very soon and reverted to the original benzolactam. A second attempt to nitrosate *3b* in absolute ether resulted in yellow crystals that tested qualitatively as a nitroso compound. A third attempt to nitrosate *3b* in dry benzene did not yield any indazole derivative after standing for a week. This suggests that an unstable *N*-nitroso derivative was obtained which probably rearranged to a *C*-nitroso product since it was not possible to rearrange to the strained *trans*-diazoester (*7b*).

A further study of the nitrosation of *3b* with nitrous anhydride in deuterochloroform indicated that, at least by the time the NMR spectra had been recorded, all *N*-nitrosolactam (*5b*) had rearranged to 6-nitroso-5,8-dimethylhydrocarbostyril (*6b*). When nitrosation of *3b* was carried out in trifluoroacetic acid-trifluoroacetic anhydride evidence for both *N*-nitroso-5,8-dimethylhydrocarbostyril (*5b*) and 6-nitroso-5,8-dimethylhydrocarbostyril (*6b*) was obtained with the NMR.

Nitrosation of hydrocarbostyril (*3c*) in methanol followed by addition of β-naphthol gave a red product, not the azo coupling product, but most likely *N*-(2-hydroxy-1-naphthyl)-1,2-naphthoquinone-1-imine. This same red com-

pound was prepared along with some 1-nitroso-2-naphthol by reacting β-naphthol with nitrous acid. The above nitrosation of hydrocarbostyril had given *N*-nitrosohydrocarbostyril which released its *N*-nitroso group to β-naphthol. A second nitrosation of hydrocarbostyril (*3c*) in trifluoroacetic acid-trifluoroacetic anhydride gave 6,8-dinitrosohydrocarbostyril. A third nitrosation of hydrocarbostyril in trifluoroacetic acid-trifluoroacetic anhydride containing some triethylamine gave only 6-nitrosohydrocarbostyril (*6c*).

Both 6,9-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one and hydrocarbostyril were prepared by the Schmidt reaction of 5,8-dimethyltetralone-1 and indanone-1, respectively, with sodium azide and methane sulfonic acid. However, the Schmidt reaction of 4,7-dimethylindanone-1 (*1b*) gave more 5,8-dimethylhydroisocarbostyril (*2*) than the expected product, 5,8-dimethylhydrocarbostyril (*3b*). This unusual result was also observed by Lansbury.[3] A careful chromatographie analysis of the mixed benzolactam gave a ratio of 81 to 19 in favor of *2* compared to the earlier reported ratio of 63 to 37.

In *N*-nitroso-6,9-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one the nitroso group lies out of the plane of the rings with its nitrogen oxygen double bond held perpendicular to the rings by the *peri* methyl and 3-methylene group. The protons of the *peri* methyl groups show an upfield shift due to their location above the plane of the nitroso group. The effect is more pronounced in *N*-nitroso-5,8-dimethylhydrocarbostyril.

In 6,8-dinitrosohydrocarbostyril the aromatic hydrogen in position seven flanked by two *ortho* nitroso groups has its chemical shift downfield to the proton in position 5. The absence of the NH proton in the 8 to 9 range and presence of a sharp singlet at 0.44 ppm is difficult to explain.

EXPERIMENTAL

5,8-Dimethyltetralone-1 (*1a*). Using a molar ratio of 1.1/1.0/2.24 of *p*-xylene, succinic anhydride, and anhydrous aluminum chloride, 3-(2,5-dimethylbenzoyl) propionic acid, m.p. 77—79°, (72 %) was prepared. Clemmensen reduction gave 4-(2,5-dimethylphenyl) butyric acid, b.p. 161° (0.5 mm), (58 %). Cyclodehydration with polyphosphoric acid yielded *1a* (51 %), m.p. 27°, b.p. 123° (1.25 mm).

4,7-Dimethylindanone-1 (*1b*). To 160 g anhydrous aluminum chloride in 625 ml of carbon disulfide a solution of 100 ml of β-chloropropionyl chloride, 123 ml of *p*-xylene, and 125 ml of carbon disulfide were added so that temperature was kept below 30°. After standing 3 h the solvent was removed. Then 1250 ml of conc. sulfuric acid was added and the batch heated for an hour at 90°. After pouring into ice the product was extracted with benzene. The benzene layer was washed with sodium carbonate and then evaporated to give *1b* (60 %), m.p. 72—74°, after recrystallization from methanol; NMR ($DCCl_3$) δ 2.30 (s, 3), 2.68 (s, 3, CH_3 *peri* CO), 2.6—3.1 (m, 4), 7.02, 7.26 (AB, $J=8$ Hz).

6,9-Dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (*3a*). Sodium azide (3.52 g) was added in 30 min to a solution of 7.7 g of 5,8-dimethyltetralone-1 (*1a*) in 100 g of methanesulfonic acid with cooling. After stirring for several hours the solution was poured on ice, extracted with ethyl acetate to give 5.17 g (68 %) *3a*, m.p. 148—151°. Recrystallized from alcohol, m.p. 153—155°.

5,8-Dimethylhydrocarbostyril (*3b*) *and 5,8-dimethylhydroisocarbostyril* (*2*). The Schmidt reaction of 14.08 g of sodium azide, 25.6 g of 4,7-dimethylindanone-1 and 270 ml of methanesulfonic acid gave two products. Recrystallization of crude ethyl acetate extract from methanol gave 1.0 g *3b*, m.p. 173.7—175.3°; IR ($CHCl_3$) 1665 cm^{-1}. The aqueous layer after ethyl acetate extraction was made basic with sodium carbonate to yield *2*, m.p. 133—134°; IR ($CHCl_3$) 1658 cm^{-1}. Chromatographic analysis of the crude product of another reaction showed 81 to 19 in favor of *2*.

Reaction of 5,8-dimethylhydrocarbostyril (3b) with nitrous oxide in acetic acid-acetic anhydride. Nitrous anhydride was added for 30 min to a cold solution of 0.7015 g *3b* in 6.9 ml acetic acid, 2.4 ml acetic anhydride, and 0.4 ml pyridine until solution became dark green. The yellow precipitate formed when the solution was poured over ice lost its yellow color rapidly and yielded 0.562 g starting material *3b*, m.p. 165–172°.

Reaction of 5,8-dimethylhydrocarbostyril (3b) with nitrous oxide in absolute ether. After 30 min of adding nitrous anhydride to 0.5 g of *3b* in 5 ml of cold ether the lactam dissolved and the solution turned dark green. Slow evaporation of ether gave bright yellow crystals which gave a positive nitroso test with conc. sulfuric acid and phenol, but no coloration with potasium iodide in acetic acid. The crystals turned black on melting at 230°.

Nitrosation of 5,8-dimethylhydrocarbostyril (3b) in deuterochloroform. Nitrous anhydride was bubbled through a solution of 0.108 g of *3b* in 1 ml deuterochloroform until dark green in 40 min. The appearance of singlets at $\delta=2.42$ and 2.32, a single aromatic proton at 7.65, and NH proton at 8.50 confirmed the product was 6-nitroso-5,8-dimethylhydrocarbostyril (*6b*) (Table 1).

Table 1. NMR data, δ ppm.

Compound	Solvent	R_1	R_2	n	R_1	R_2	$(CH_2)_n$	NH	Aromatic
2	$CDCl_3$				2.25	2.68	2.92–3.41	7.25	7.02, 7.16 (AB, $J=8$ Hz)
3a	$DCCl_3$	CH_3	CH_3	3	2.28	2.28	2.2–2.9	8.90	6.93
3b	$DCCl_3$	CH_3	CH_3	2	2.23	2.23	2.5–2.9	8.30	6.78, 6.92 (AB, $J=8$ Hz)
3b	CF_3COOH / $(CF_3CO)_2O$	CH_3	CH_3	2	2.25	2.25	2.85 (broad)	9.50	6.86
3c	CF_3COOH	H	H	2	—	—	3.08	9.92	7.15
4	$CDCl_3$				2.30	2.72	2.92(t, $J=6$ Hz) 3.92(t, $J=6$ Hz)	—	7.15, 7.29 (AB, $J=8$ Hz)
5a	$CDCl_3$	CH_3	CH_3	3	2.31	1.82	2.2–2.7	—	7.08, 7.22 (AB, $J=8$ Hz)
6b	$CDCl_3$	CH_3	CH_3	2	2.42	2.32	2.6–3.2	8.50	7.65 (Singlet)
6c	CF_3COOH / $(CF_3CO)_2O$ / $N(C_2H_5)_3$	H	H	2	—	—	3.2	8.2	7.2

Nitrosation of 5,8-dimethylhydrocarbostyril (3b) in trifluoroacetic acid-trifluoroacetic anhydride. Nitrous anhydride converted 0.1 g *3b* in 0.75 ml trifluoroacetic acid and 0.25 ml of trifluoroacetic anhydride into a mixture of *N*-nitroso-5,8-dimethylhydrocarbostyril (5b). NMR δ 2.26 (R_1) and 0.44 (R_2), and 6-nitroso-5,8-dimethylhydrocarbostyril (*6b*), NMR δ 2.60 (R_1) and 2.36 (R_2); 2.8–3.3 (methylene protons); 9.48 (NH); 7.7 and 8.4 (aromatic protons) (Table 1).

Attempted preparation of 6-methyl-7-(β-carboxyethyl)-1H-indazole. Nitrous anhydride was bubbled through an ice-cold suspension of 0.155 g of 5,8-dimethylhydrocarbostyril (*3b*) in 3 ml of benzene until the solution turned green. The solution was filtered and aspirated until yellow. Anhydrous sodium sulfate was added. After a week the benzene was extracted with 3 ml of 2 N hydrochloric acid and the aqueous layer made barely basic with ammonia. No indazole derivative crystallized out.

Attempted azo coupling of hydrocarbostyril (3c). Nitrous anhydride was added to a cold suspension of 0.53 g *3c* in 25 ml of absolute methanol until slightly green. Decantation of solution into 0.422 g of β-naphthol in 3 ml of methanol gave overnight dark red crystals. Recrystallized from benzene-ethanol (2:1; v/v), m.p. 274–276°. (Found: N 4.37. Calc. for $C_{20}H_{13}NO_2$: N 4.69.) The nitrosation of β-naphthol gave a red tar and yellow

crystals (α-nitroso-β-naphthol). The red tar had the same retention time on alumina as the red crystals above.

Nitrosation of hydrocarbostyril (*3c*). Nitrosation of *3c* in a 3:1 trifluoroacetic acid-trifluoroacetic anhydride gave 6,8-dinitrosohydrocarbostyril, NMR δ 3.04 (m, 4) methylene protons; 7.20 (s, 1, aromatic proton in position 5); 8.20 (s, 1, aromatic proton in position 7); 0.44 (s, 1).

A second nitrosation of 0.8 g of *3c* in 5.70 ml trifluoroacetic acid, 1.98 ml trifluoroacetic anhydride, and 0.33 ml of triethylamine gave 6-nitrosohydrocarbostyril (*6c*), NMR δ 8.2 (s, 1, NH); 7.2 (m, 3, aromatic protons); 3.2 (4 by subtracting CH_2 of $N(CH_2CH_3)_3$); 1.4 (t, methyl of triethylamine); 11.8 (proton of trifluoroacetic acid) (Table 1).

Nitrosation of 5,8-dimethylhydroisocarbostyril (*2*). Nitrous anhydride generated by dropping conc. sulfuric acid with 3 % nitric into solid sodium nitrite was bubbled through and ice-cold solution of 0.1489 g of *2* in 1.47 ml of glacial acetic acid, 0.51 ml of acetic anhydride, and 0.09 ml of pyridine until the solution turned dark green in about 10 min. After pouring on ice a yellow precipitate was dried to give 0.1574 g (88 %) of *N*-nitroso-5,8-dimethylhydroisocarbostyril (4), m.p. 76—77° after recrystallization from methanol, NMR ($DCCl_3$) δ 2.30 (s, 3), 2.72 (s. 3), 2.92 (t, 2, $J=6$ Hz, $CH_2C_6H_5$), 3.91 (t, 2, $J=6$ Hz, CH_2NNO), 7.15, 7.29 (AB, $J=8$ Hz) (Table 1).

N-*Nitroso-6,9-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one* (*5a*). Nitrous anhydride was added to 1.89 g 6,9-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (*3a*) dissolved in 12 ml of pyridine until it turned green. After pouring on ice 2.01 g of *5a* (92 %), m.p. 102° were obtained.

6-Methyl-7-(γ-carboxypropyl)-1H-indazole (*8*). *N*-Nitroso-6,9-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (*5a*) (2.18 g) was allowed to stand in dry benzene for a week. Three extractions with dilute hydrochloric acid followed by careful neutralization with ammonia gave 1.303 g (65 %) of *8* recrystallized from methanol, m.p. 177—178°. (Found: C 65.82; H 6.46; N 12.68. Calc. for $C_{12}H_{14}O_2N_2$: C 66.03; H 6.47; N 12.84). NMR (DMSO) δ 2.32 (s, 3), 2.32 (t, 2), 2.88 (t, 2, $J=7$ Hz), 1.98 (m, 2) 7.04—7.60 (AB, $J=8$ Hz), 8.1 (s, 1). NMR ($DCCl_3$) δ 2.42 (s, 3), 2.60 (t, 2), 3.02 (t, 2, $J=7$ Hz), 1.96 (m, 2), 7.09—7.59 (AB, $J=8$ Hz), 8.0 (s, 1), 12.94 (s, 1).

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