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THERMOLYSIS OF N-SUBSTITUTED BENZAZOCINE HYDROCHLORIDES

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Heating 1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocine (1) hydrochloride (pentazocine hydrochloride) in silicon oil or diphenyl ether gave the secondary amine (3) which was formed by an elimination of 3-methyl-2-butenyl group on nitrogen in a moderate yield. The same secondary amine (3) was also obtained from several N-substituted benzazocine derivatives (4, 5 and 6).

It has been well known that N-substituted benzazocine derivatives, especially 1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocine (1), namely pentazocine, show an effective analgesic activity. We have investigated a synthesis of pentazocine by several methods[1,2,3] and also reported

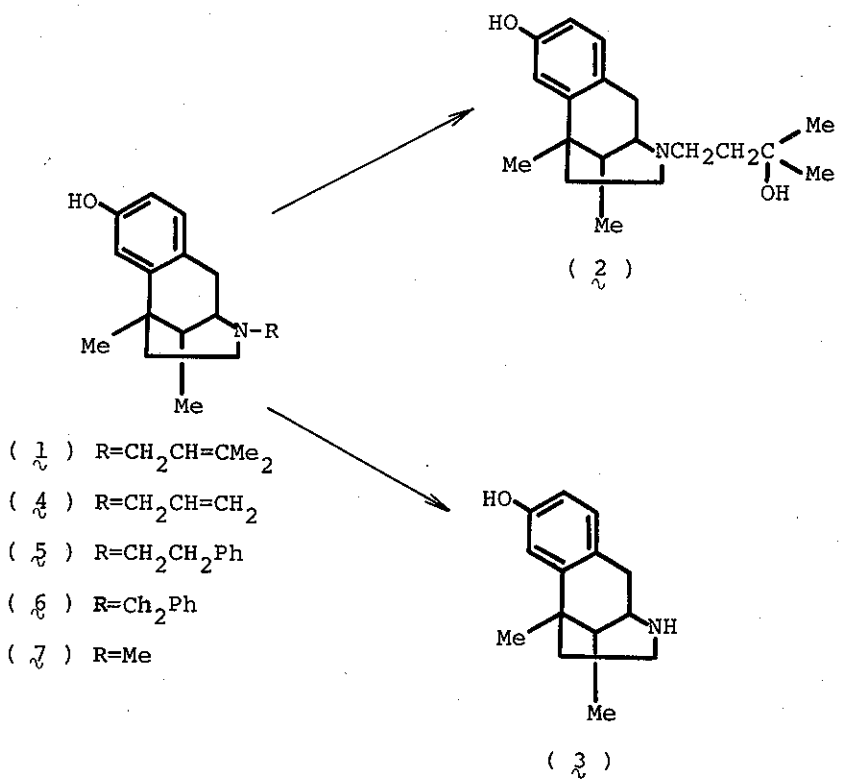
chemical and physical properties of 1.[4] For example, heating pentazocine 1 in diluted hydrochloric acid afforded the hydrated product (2) in a good yield, whose reaction was investigated from a kinetical point of view. In a continuation of this work, we examined a reactivity of pentazocine (1) hydrochloride[5] and related compounds in case of heating in nonpolar solvent or without solvent and found an interesting reaction which is different from a reaction in aqueous solution. Here we wish to report our simple but interesting result.

Firstly we investigated a chemical behaviour of pentazocine (1) hydrochloride in nonpolar solvents. Thus, heating a suspension of pentazocine hydrochloride (0.5 g) in silicon oil (20 ml) at 260° for 10 min with stirring gave, in 69 % yield 1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-3-benzazocine (3) hydrochloride, mp 292 - 294° (decomp.), in which 3-methyl-2-butenyl group on nitrogen atom of 1 was eliminated, by accompanying a decomposition. The structure of this product was determined by comparisons of spectral data with an authentic sample.[5,6] The same reaction of pentazocine (1) hydrochloride in diphenyl ether[7] also gave the N-dealkylated 3-benzazocine (3) hydrochloride in almost similar yield. In these reactions, 3-methyl-2-butenyl group on nitrogen atom would be eliminated as an isoprene molecule.

Chart 1

Similarly, N-allyl-(4)[8], N-phenethyl-(5)[9], and N-benzyl-3-benzazocine (6)[6] hydrochlorides have transformed to the dealkylated

Chart 1



(1) R=$CH_2CH=CMe_2$

(4) R=$CH_2CH=CH_2$

(5) R=CH_2CH_2Ph

(6) R=Ch_2Ph

(7) R=Me

(2)

(3)

secondary amine (3) hydrochloride in 43 %, 19 % and 12 % yield by heating in diphenyl ether, respectively. However, N-methyl-3-benzazocine (7)[10] hydrochloride did not give 3 but a tarry substance under the same reaction conditions.

Furthermore, a fusion of pentazocine (1) hydrochloride also gave, in 75 % yield, the N-dealkylated secondary amine (3) hydrochloride.

As mentioned above, it is of interest that heating pentazocine (1) in diluted hydrochloric acid afforded the hydration product (2), but fusion of the corresponding hydrochloride or heating in nonpolar solvent gave the N-dealkylated product (3). We are now investigating a scope and limitation of this type of an N-dealkylation reaction[11] on tertiary amines.

References

1. T. Kametani, K. Kigasawa, M. Hiiragi, and N. Wagatsuma, Heterocycles, 1974, 2, 79.

2. D. C. Palmer and M. J. Strauss, Chem. Rev., 1977, 77, 1.

3. Our recent synthesis using cyclopropanones will be published in following journal; T. Kametani, H. Seto, H. Nemoto, and K. Fukumoto, J. Org. Chem., Vol. 42, in 1977, in press.

4. K. Kigasawa, H. Shimizu, K. Ohkubo, and R. Shoji, J. Pharm. Soc. Japan, 1976, 96, 1342.

5. E. M. Fry and E. L. May, J. Org. Chem., 1959, 24, 116.

6. T. Kametani, K. Kigasawa, M. Hiiragi, T. Hayasaka, N. Wagatsuma, and K. Wakisaka, J. Heterocyclic Chem., 1969, 6, 43.

7. T. Kametani, S. Takano, S. Hibino, and M. Takeshita, Synthesis, 1972, 475.

8. Brit. Pat., 921,547 (1963, March, 20) [Chem. Abstr., 1967, 61, 4325^{f}]; T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, T. Uryu, and H. Sugi, J. Heterocyclic Chem., 1973, 10, 27.

9. T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, S. Saitoh, and H. Sugi, J. Heterocyclic Chem., 1973, 10, 313.

10. E. L. May and E. M. Fry, J. Org. Chem., 1957, 22, 1366.

11. Houben-Weyl, "Methoden der Organischen Chemie", 4th ed. 1957, Vol. 11, pt. 1, p. 961.

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