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Benzocycloalkanones in the Schmidt Reaction

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When the Schmidt reaction is carried out with conc. hydrochloric acid as solvent and as catalyst, α-tetralone yields the tetrazole *X*, and 5,6,8,9-tetrahydrobenzo-7H-cyclohepten-5-one *II* yields the lactam *IV*. The structure of the tetrazole has been established by the UV-spectrum and through a new reaction which involves a destructive reduction of the tetrazole ring with $LiAlH_4$, yielding the known tetrahydrobenzo[c]azepin *VIII*.

The influence of the reaction conditions on the direction of the Schmidt reaction is briefly discussed.

In a research programme for the development of new pharmaceuticals we required some benzazocines and benzazepines. A useful route to cyclic amines is to submit a cyclic ketone to the Schmidt reaction,[1] and to reduce the formed lactam with $LiAlH_4$.[2] An amine is obtained having a ring size one atom greater than the starting ketone.

Some benzocycloalkanones were thus reacted with hydrazoic acid in the molar ratios 1:1 and in the presence of concentrated hydrochloric acid according to the procedure described by Schmidt *et al.*[3] for acid-soluble aminoalkyl-substituted ketones.

With this variation of the Schmidt reaction, 5,6,8,9-tetrahydrobenzo-7H-cyclohepten-7-one *I* [4] and 5,6,8,9-tetrahydrobenzo-7H-cyclohepten-5-one *II* [4] gave the lactams *III* and *IV*, respectively.

When, however, α-tetralone *V* was reacted under these conditions a product with the m.p. 100—101° was obtained, Substance A. The expected 2,3,4,5-tetrahydrobenzo[b]azepine-2-one *VI* has the m.p. 141—142°,[5] whereas 2,3,4,5-tetrahydrobenzo[c]azepine-1-one *VII* has the m.p. 100°.[6] According to these melting points, it was tentatively assumed that Substance A has the structure *VII*. Substance A was reduced with $LiAlH_4$, and an amine, identified as 1,2,3,4-tetrahydrobenzo[c]azepine *VIII*, was obtained. The elemental analysis of Substance A, however, corresponds to the empirical formula $C_{10}H_{10}N_4$. This excludes structure *VII* for Substance A.

A side reaction in the Schmidt reaction is the formation of tetrazoles.[1,7,8] A tetrazole derivative of α-tetralone has the molecular formula $C_{10}H_{10}N_4$, and accordingly a tetrazole derivative of α-tetralone is predicted for Substance

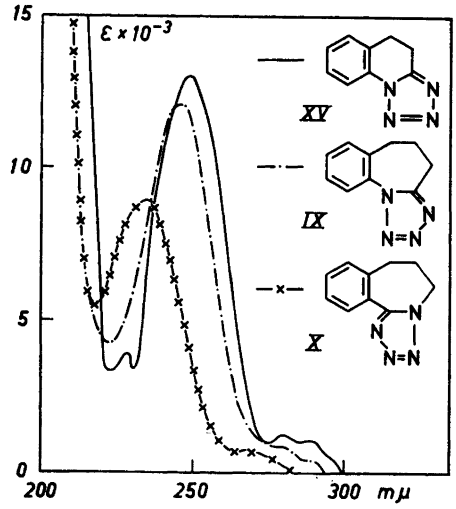


Fig. 1. UV-spectra in ethanol. Compound *IX* 5,6-dihydro-4H-tetrazolo[4,5-a]benzo-[f]azepine according to Huisgen *et al.*[9]; Compound *X* 6,7-dihydro-5H-tetrazolo-[4,5-a]benzo[c]azepine (Substance A); Compound *XV* 4,5-dihydro-tetrazolo-[4,5-a]quinoline according to Huisgen *et al.*[9]

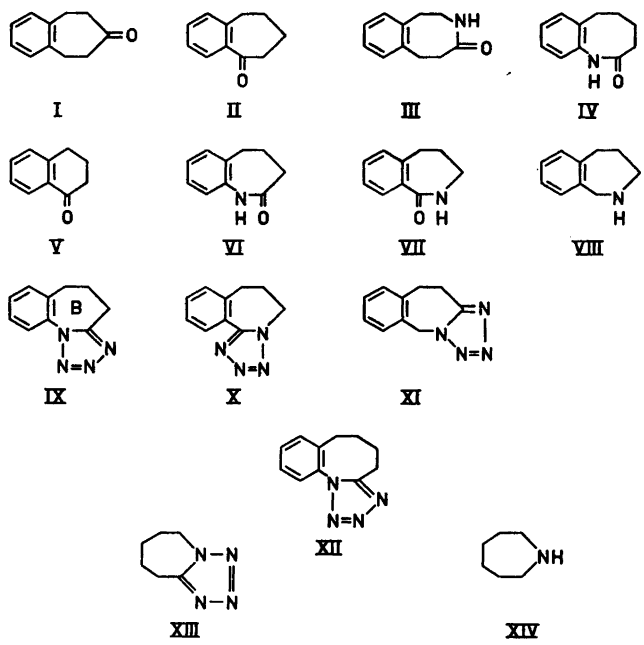
A. In scheme 1 the three possible tetrazoles *IX*, *X* and *XI* are outlined. The UV-spectrum of Substance A (Fig. 1) exhibits a minimum at 222 mμ, a maximum at 245 mμ and a shoulder at 280 mμ.

Huisgen *et al.*[9] have synthesized 5,6-dihydro-4H-tetrazolo[4,5-a]benzo[f]-azepine *IX* (m.p. 104°) and discuss the UV-spectra of this compound together with other tetrazoles differing from those mentioned above in the size of the B-ring. These authors conclude that when ring B has a size of six or seven atoms a strong band is present in the 230—250 mμ region and that this band arises from conjugation between the benzene and tetrazole rings. As Substance A, predicted to be a tetrazole derivative of α-tetralone, has an absorbtion band in the same region as Huisgen's compound, and as the complete spectrum resembles that of Huisgen's compounds (Fig. 1), it can be concluded from this and the other evidence that Substance A is a tetrazole, and that the tetrazole ring is conjugated with the benzene ring. We therefore propose one of the structural formulas *IX* or *X* for Substance A. Structure *XI* is excluded as there is no possibility for conjugation between the benzene ring and the tetrazole ring as indicated in the UV-spectra.

$LiAlH_4$-reductions of tetrazoles have, as far as we know, not been previously described, the following reaction was used to verify the course of the reaction. Pentamethylenetetrazole *XIII* was reacted with $LiAlH_4$ in di-isopropyl ether. The isolated product could be identified as heptamethylenimine *XIV*. It is thus shown that this reaction proceeds without rupture or rearrangement of the azepine ring.

As the reduction product of Substance A is 1,2,3,4-tetrahydrobenzo[c]-azepine *VIII*, Substance A must contain the benzo[c]azepine skeleton and thus have the structural formula *X*.

Huisgen [10,11] has reported that, with the normal Schmidt reaction, *i.e.* hydrazoic acid, benzene and sulphuric acid, α-tetralone yields the lactam *VI*,



Scheme 1.

whereas 5,6,8,9-tetrahydro-7H-benzocycloheptene-5-one *II* yields the tetrazole *XII*.

These results are in sharp contrast to those obtained with the variation of the Schmidt reaction used in this work. Huisgen points out that the differences in directions of reactions in his series of benzocycloalkanones are caused by effects dependent on the ring size. This is also true (according to our present knowledge) for our series, with the exception that these effects cause the reactions to go in the opposite direction to that expected from Huisgen's work. The conditions thus play an important role in determining the direction of the Schmidt reaction with benzocycloalkanones.

EXPERIMENTAL

6,7-Dihydro-5H-tetrazolo[4,5-a]benzo[c]azepine X. 13.7 g (0.2 mole) of sodium azide were added in small portions at 2°C to a stirred mixture of 29.2 g (0.2 mole) of α-tetralone and 150 ml of conc. hydrochloric acid. The temperature was kept at 2°C for 2 h and then held at room temperature for another 2 h. The mixture was poured into ice-water and neutralized with potassium carbonate. The reaction mixture was extracted with two portions of chloroform. The combined chloroform layers were dried and the solution evaporated to dryness. The residue was dissolved in warm ether and petroleum ether added to the point of precipitation. After chilling, 13.8 g of a crystalline product, m.p. 88–92°, were collected. 13 g of α-tetralone were recovered from the mother liquor. Repeated recrystallisations from ethanol yielded a dimorphous substance with m.p. 94.5–95.5° and 99–100°. (Found: C 64.6; H 5.4; N 30.4. Calc. for $C_{10}H_{10}N_4$: C 64.50; H 5.41; N 30.09).

1,2,3,4-Tetrahydrobenzo[c]azepine VIII. 6.0 g (0.031 mole) of 6,7-dihydro-5H-tetrazolo-[4,5-a]benzo[c]azepine *X* and 1.5 g (0.04 mole) of $LiAlH_4$ were refluxed for 10 h in 150 ml of dry ether. The reaction mixture was hydrolyzed with water and sodium hydroxide. The precipitated aluminate was filtered off and washed with ether. The combined ether solutions were concentrated *in vacuo* and the residue was distilled under reduced pressure. A fraction boiling at 107–108°/8 mm Hg was collected, yield 3 g, n_D^{20} 1.563. Hydrochloride from ether m.p. 223–225°. (v. Braun *et al.*[12] report no m.p. as their preparation was deliquescent). (Found: C 65.6; H 7.6; N 7.5; Cl 19.5. Calc. for $C_{10}H_{14}NCl$: C 65.39; H 7.68; N 7.63; Cl 19.30). Chloroplatinate from water, m.p. 194–196°, reported [12] 192°, toluenesulphonate from ethanol, m.p. 134–136°, reported [13] 135°.

1,2,3,4,5,6-Hexahydrobenzo[d]azocine-4-one III. 10.5 g (0.16 mole) of sodium azide were added in small portions to a stirred mixture of 16 g (0.1 mole) of 5,6,8,9-tetrahydro-7H-benzocycloheptene-7-one and 75 ml of conc. hydrochloric acid held below 8°C. The stirred reaction mixture was held at 8° for 2 h and then at room temperature for another 2 h. The mixture was then poured into ice-water and neutralized with potassium carbonate. The precipitate formed was collected and dissolved in hot benzene and some insoluble matter discarded. Petroleum ether was added to the hot solution which brought the substance to crystallization. Yield 15.5 g, m.p. 146–147°. (Found: C 75.4; H 7.6; N 7.9. Calc. for $C_{11}H_{13}NO$: C 75.39; H 7.48; N 8.00). An identical specimen was synthesized from the same ketone as above by the Beckman rearrangement of the appropriate oxime, m.p. 125–127°.

1,2,3,4,5,6-Hexahydrobenzo[b]azocine-2-one IV. 30 g (0.187 mole) of 5,6,8,9-tetrahydro-7H-benzocycloheptene-5-one were reacted with 16.3 g (0.25 mole) of sodium azide in 180 ml of conc. hydrochloric acid and worked up as described above with the exception that chloroform was used instead of benzene. Yield 29 g, m.p. 154–156°, reported [11] 154–155°. (Found: C 75.3; H 7.4; N 8.1. Calc. for $C_{11}H_{13}NO$: C 75.39; H 7.48; N 7.99).

Hexamethylenimine XIII. 10 g (0.0736 mole) of pentamethylenetetrazole (Ed *XI*) and 4.3 g (0.1 mole) of $LiAlH_4$ were refluxed in 25 ml of di-isopropyl ether for 24 h. The reaction mixture was hydrolysed with sodium hydroxide and water, and the precipitated aluminate was filtered off and washed with ether. Ethanolic hydrogen chloride was added to the combined ether solutions. The precipitated hexamethylenimine hydrochloride was collected on the filter and washed with ether. Yield 8.5 g, m.p. 234–236°, reported 236°.[14] Picrate, m.p. 145–147°, reported [14] 146.5°.

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