598. *Approaches to Azaheptacyclic Compounds.*

By A. H. Rees.

Attempts to enlarge the ring of *p*-quinones by the Beckmann and the Schmidt reaction failed, but enlarging the ring of cyclohexa-1,4-dione monoketal led to new nitrogen heterocyclic compounds. It was not possible to shorten the synthesis of 2,5-dihydro-7,8-dimethyl-2,5-dioxobenz[*f*]azepine.

The product of rearrangement of *p*-benzoquinone monoxime, reported by Beckmann and Liesche [1] to be 2,5-dihydro-2,5-dioxoazepine (I; R = H) was in fact *pp'*-dihydroxyazoxybenzene.[2]

As the benzazepine (II) [3] is known, compounds such as (I; R = alkyl) should exist. The Beckmann rearrangement of *o*-alkyl-*p*-quinones was therefore attempted in the hope that steric hindrance would restrict coupling and facilitate ring expansion. The two monoximes of thymoquinone however gave phenolic products.[2]

By the Schmidt reaction thymoquinone gave a neutral substance, whose infrared spectrum showed a cyanide band, 2,5-*p*-xyloquinone did not give an analogous product, and *p*-benzoquinone merely oxidised azide ion to nitrogen.

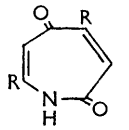
Perhydroazepin-2,5-dione (III) was sought as an intermediate for the preparation of the dione (I; R = H). As cyclohexa-1,4-dione monoxime was not readily obtained, the monoketal oxime (IV; R = H) was used; Beckmann rearrangement was accompanied by deketalisation. The toluene-*p*-suphonyl ester (IV; R = Ts) was rearranged and hydrolysed in pyridine to yield, *via* the ketal-lactim toluenesulphonate, the trimethylene ketal of (III), which, on further hydrolysis, gave the ketolactam (III); this, however, could not be converted into the azepine (I; R = H).

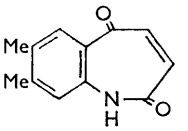
As an alternative protecting group, catechol was used to make the monoketal (V) which was likewise expanded to the *o*-phenylene ketal of the dione (III).

2,5-Dihydro-7,8-dimethyl-2,5-dioxobenz[*f*]azepine (II) was required in quantity [4] and because removal of the benzene ring was a potential route to (I). To try to shorten its

[1] Beckmann and Liesche, *Ber.*, 1923, **56**, 1.
[2] Raphael and Vogel, *J.*, 1952, 1958.
[3] Rees, *J.*, 1959, 3111.
[4] James Dinah M. and Rees, to be published.

synthesis, *N*-acetyl-3,4-xylidine was β-carboxyacryloylated giving the expected amide (VI; R = Ac), whose orientation was confirmed by hydrogenation to the known dihydro-compound.[3] The amide gave on acid hydrolysis the amino-acid (VI; R = H) though in poor yield since the benzoylacrylic side chain is not very stable to acid.[5] The amino-acid


(I)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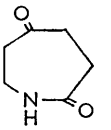
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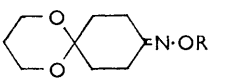
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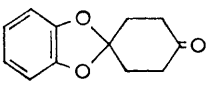
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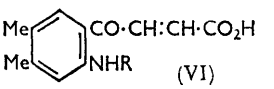
(VI)

could not be cyclised to the lactam (II). Alkaline hydrolysis of the amide gave a poor yield of the amino-acid and a low yield of 1,2-dihydro-6,7-dimethyl-2-oxoquinoline-4-carboxylic acid, presumably *via* a Camps quinoline synthesis [6] with side-chain degradation.

The infrared spectra of all new compounds were in accord with the suggested structures.

Experimental

Thymoquinone Mono-oximes.—These were prepared by the nitrosation [7] of thymol and carvacrol and converted (acid chloride–pyridine) into their *benzenesulphonyl derivatives*, m. p.s 75° and 97°, respectively (from cyclohexane) [Found: (*a*) N, 4·4; S, 9·6; (*b*) N, 4·5; S, 10·0. $C_{16}H_{17}NO_4S$ requires N, 4·4; S, 10·0%).

Reaction of Thymoquinone with Hydrazoic Acid.—Smith's method [8] with trichloroacetic acid gave a substance, m. p. 174° (from alcohol) (Found: C, 62·5; H, 6·3; N, 14·9; O, 16·5%; *M*, 176. $C_{10}H_{12}N_2O_2$ requires C, 62·5; H, 6·3; N, 14·6; O, 16·6%; *M*, 192); $\lambda_{max.}$ 270 mμ, ν 4·5 μ (sh) (assigned to a nitrile). It was neutral and did not react with Brady's reagent.

Reaction of p-*Benzoquinone with Azide Ion.*—Benzoquinone was stirred with a solution of sodium azide. Nitrogen was evolved and after acetylation, quinol diacetate, m. p. and mixed m. p. 123°, was obtained.

Reaction of 1,3-*Dioxan-2-spirocyclohexan-4'-one Oxime* (IV; R = H).—The ketone [9] was converted into the *oxime* under neutral or alkaline conditions. This had b. p. 155°/4 mm., m. p. 93° (from cyclohexane) (Found: C, 58·6; H, 8·25; N, 7·3. $C_9H_{15}NO_3$ requires C, 58·4; H, 8·2; N, 7·6%). Treatment with toluene-*p*-sulphonyl chloride in pyridine below 15° gave the *oxime ester* (IV; R = *p*-Me·C_6H_4·SO_2), m. p. 109° (from benzene) (Found: C, 56·3; H, 6·4; N, 4·0; S, 8·9. $C_{16}H_{21}NO_5S$ requires C, 56·6; H, 6·25; N, 4·1; S, 9·4%).

When the mother-liquor was kept or when esterification was at higher temperature, a second ester was sometimes obtained; this had m. p. 127° (from benzene–cyclohexane) and an infrared spectrum very similar to but not identical with that of the first ester; it was probably 3,4,5,6-tetrahydro-7-toluene-*p*-sulphonyloxy-4,4-trimethylenedioxy-2*H*-azepine.[10]

Perhydro-5,5-trimethylenedioxyazepin-2-one.—The crude oxime ester (IV; R = *p*-C_6H_4Me·SO_2) (4 g.) was warmed in pyridine for 6 hr. Addition of water, extraction with chloroform, and removal of the solvent from the dried extract gave an oil (1·4 g.) which partly solidified. The solid when sublimed and recrystallised from benzene–cyclohexane gave a hygroscopic *lactam*, m. p. 87° (Found: C, 58·05; H, 7·8; N, 8·2. $C_9H_{15}NO_3$ requires C, 58·35; H, 8·15; N, 7·6%).

Perhydroazepine-2,5-dione (III).—The ketal (1 g.) in propanol was heated for 20 min. on a

[5] Bogert and Ritter, *J. Amer. Chem. Soc.*, 1925, **47**, 527.
[6] Camps, *Ber.*, 1899, **32**, 3228.
[7] Kremers, Wakeman, and Hixon, *Org. Synth.*, Coll. Vol. I, 2nd edn., p. 511.
[8] Smith, *J. Amer. Chem. Soc.*, 1948, **70**, 320.
[9] Rothe and Woodward, personal communication.
[10] Cf. Oxley and Short, *J.*, 1948, 1514.

steam-bath with 2N-sulphuric acid (1 ml.), and the solution then neutralised with sodium hydrogen carbonate and extracted with chloroform. After evaporation of the sovent, the oily keto-lactam (III) remained; ν 1650 cm.$^{-1}$ (lactam) and 1710 cm.$^{-1}$ (ketone). Its *dinitrophenylhydrazone* had m. p. 234° (from dioxan) (Found: C, 46·7; H, 4·2; N, 22·7. $C_{12}H_{13}N_5O_5$ requires C, 46·9; H, 4·25; N, 22·8%).

1,3-*Benzodioxin*-2-*spirocyclohexan*-4′-*one* (V).—Catechol (11 g.) and cyclohexa-1,4-dione (26·4 g.) were refluxed with benzene (100 ml.), toluene-*p*-sulphonic acid (0·5 g.), and the acid chloride (0·5 g.) until water (1 ml.) separated azeotropically. The solution was filtered, giving the *diketal*, m. p. 315°, from dioxan (Found: C, 72·6; H, 5·4; O, 21·3. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4; O, 21·6%). Evaporation of the filtrate gave the *monoketal* (7 g.), m. p. 183°, from cyclohexane (Found: C, 70·4; H, 5·9. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%). The *oxime*, m. p. 135°, separated from aqueous alcohol (Found: C, 65·8; H, 6·2; N, 6·5. $C_{12}H_{13}NO_3$ requires C, 65·7; H, 6·0; N, 6·4%).

1,3-*Benzodioxin*-2-*spiro*-4′-*perhydroazepin*-7′-*one*.—The oxime was treated with benzenesulphonyl chloride in pyridine and set aside overnight. Extraction of the residue with ether and evaporation of the ether gave the *lactam*, m. p. 232° (sealed tube), from methanol (Found: C, 65·9; H, 6·1; N, 6·3%; *M*, 240. $C_{12}H_{13}NO_3$ requires C, 65·7; H, 6·0; N, 6·4%; *M*, 219).

2-β-*Carboxyacryloyl*-4,5-*dimethylacetanilide* (VI; R = Ac).—This was prepared in 60% yield by the method used for the corresponding β-carboxypropionyl derivative.[3] It had m. p. 198° (from aqueous alcohol) (Found: C, 64·8; H, 5·7; N, 5·4. $C_{14}H_{15}NO_4$ requires C, 64·4; H, 5·8; N, 5·4%). From the aqueous filtrate, fumaric acid was obtained by acidification, suggesting that the *anilide* itself, also had the *trans*-configuration.

Hydrogenation of the Acid (VI; R = Ac).—The acid in propanol, with Adams catalyst, took up slightly more than the theoretical volume of hydrogen. Filtration, evaporation, and crystallisation gave material, m. p. 178°, undepressed by an authentic sample of the carboxypropionyldimethylacetanilide.[3]

2-β-*Carboxyacryloyl*-4,5-*dimethylaniline* (VI; R = H).—The acetyl derivative (VI; R = Ac) was hydrolysed with acid, giving the *amino-acid* (VI; R = H), m. p. 180° (from aqueous alcohol) (Found: C, 65·3; H, 6·0; N, 6·4. $C_{12}H_{13}NO_3$ requires C, 65·7; H, 6·0; N, 6·4%).

Action of Alkali on the Acid (VI; R = Ac).—The acid (VI; R = Ac) (5·2 g.) was heated overnight with 2N-alkali (30 ml.). The solution was acidified and a precipitate (3·1 g.) obtained. The mother-liquor slowly deposited an acid (0·5 g.), m. p. 360° (from aqueous propanol) (Found: C, 61·0; H, 5·8; N, 5·65. Calc. for $C_{12}H_{11}N_2O_3,H_2O$: C, 61·3; H, 5·6; N, 5·95%), undepressed by 1,2-dihydro-6,7-dimethyl-2-oxoquinoline-4-carboxylic acid.[3,11]

The precipitate (3·1 g.) was dissolved in sodium hydrogen carbonate solution and acidified, giving the starting acid (VI; R = Ac) (1·8 g.). The filtrate from this, on neutralisation, gave some amino-acid (VI; R = H) (0·1 g.).

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[11] King and Wright, *Proc. Roy. Soc.*, 1948, *B*, **135**, 271.