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An Abnormal Schmidt Reaction: 4,5-Dihydro-1*H*-1-benzazepin-2(3*H*)-one from γ-Phenylbutyric Acid

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Anomalous results were obtained when γ-phenylbutyric acid (I) was subjected to the Schmidt reaction. 4,5-Dihydro-1*H*-1-benzazepin-2(3*H*)-one (IX) was obtained in 40% yield besides 4-(3-aminopropyl)benzenesulphonic acid (III). The structure of (III) was established by chemical degradation. No cyclic lactams are formed under the same conditions from higher and lower homologues of (I).

DURING another investigation [1] it was attempted to prepare γ-phenylpropylamine (II) from γ-phenylbutyric acid (I) by the Schmidt reaction. None of the expected amine was obtained; instead an acidic and a neutral product were formed in about equal amounts.

Under the usual reaction conditions [2] a colourless solid started to separate from the reaction mixture within a few minutes; this was shown by elemental analysis to be a sulphonic acid of a phenylpropylamine. The structure was elucidated by fusion with potassium hydroxide and subsequent benzoylation of the aminophenol obtained to yield *N*-benzoyl-3-(4-benzoyloxyphenyl)propylamine (VI), identical with a specimen prepared by benzoylation of 3-(4-hydroxyphenyl)propylamine.[3] Since rearrangements during alkali fusion are not uncommon, the sulphonic acid was also oxidised with alkaline potassium permanganate to give potassium 4-carboxybenzenesulphonate (IV), which was then converted by use of chlorosulphonic acid into *p*-chlorosulphonylbenzoic acid (V), identical with an authentic sample.[4] The acidic reaction product is, therefore, 4-(3-aminopropyl)benzenesulphonic acid (III).

The neutral product was identified as 4,5-dihydro-1*H*-1-benzazepin-2(3*H*)-one (IX) by comparison with a sample prepared by an independent route.[5]

Variations of reaction temperature (40—75°C) and time 0·5—3 h) did not change products or product ratios. The combined yields of (III) and (IX) amounted to 80—90%; no trace of the expected amine (II) was detected.

The next higher homologue of (I), δ-phenylvaleric acid (X), gave, under the same conditions, exclusively 4-(4-aminobutyl)benzenesulphonic acid (XI), whose structure was established by oxidation with potassium permanganate to the carboxylic acid (IV) and subsequent transformation into the sulphonyl chloride (V). No heterocyclic lactam was detected.

The formation of 4,5-dihydro-1*H*-1-benzazepin-2(3*H*)-one (IX) (Scheme 1) can be rationalised in terms of formal attack of an intermediate positive ion (VII) [6]

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[1] S. K. Datta, Ph.D. Thesis, 1965, Indian Institute of Technology, Kharagpur, India.

[2] (*a*) M. Oesterlin, *Angew. Chem.*, 1932, **45**, 536; (*b*) H. Wolff, *Org. Reactions*, 1946, **3**, 307.

[3] G. Goldschmiedt and O. V. Fraenkel, *Monatsh.*, 1914, **35**, 383.

[4] B. A. Everard and J. A. Mills, *J. Chem. Soc.*, 1950, 3387.

[5] R. T. Conley, *J. Org. Chem.*, 1958, **23**, 1331.

[6] M. S. Newman and H. L. Gildenhorn, *J. Amer. Chem. Soc.*, 1948, **70**, 317.

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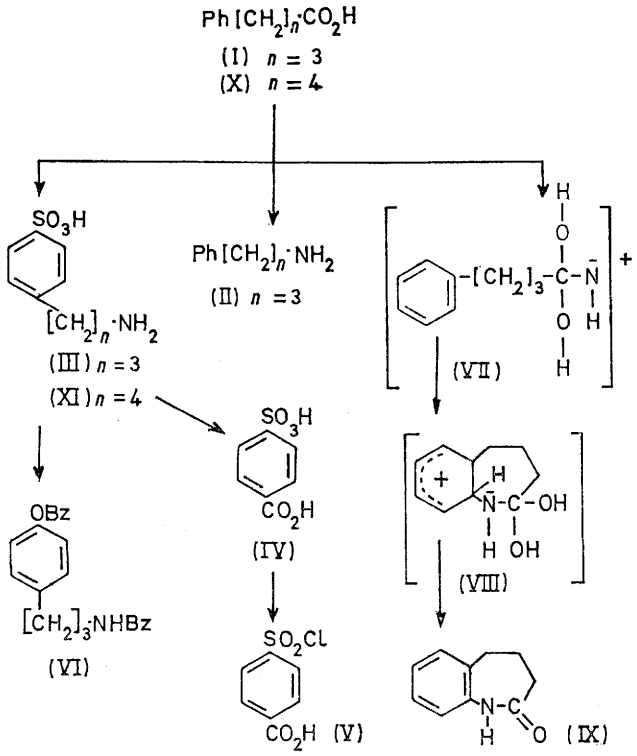
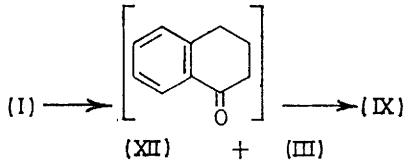
at the *ortho*-position of the benzene nucleus to form a carbonium ion (VIII), which stabilises itself as (IX) by loss of water and a proton. However, the next lower homologues of (I) ($n = 1$ or 2) give the corresponding amines (II; $n = 1$ or 2) in yields of 70—90% with no



SCHEME 1

heterocyclic lactam as a by-product;[1] steric considerations would seem to favour the formation of the stable five- (oxindole) or six- (carbostyril) membered lactams.

An alternative mechanism for the formation of (IX) from (I) (Scheme 2) involves the Schmidt reaction of α-tetralone,[5] which might be formed during the reaction by cyclisation of (I)[7] with concentrated sulphuric acid. However this mechanism is eliminated by our experimental findings. When sulphuric acid was replaced by polyphosphoric acid in the Schmidt reaction, the amine



SCHEME 2

(II) was formed in *ca.* 20% yield, but was accompanied by about as much (IX) as with sulphuric acid. Polyphosphoric acid should be a better cyclisation agent for the formation of α-tetralone (XII)[8] from (I). One would therefore expect a higher yield of (IX) and no production of amine (II) if the reaction intermediate were the tetralone (XII). This argument, however, implies that the reactions in question are thermodynamically and not kinetically controlled.

The predominant or exclusive production of the amino-sulphonic acids (III) and (XI), might be seen as the result of a diminishing protective effect of the amino-group as it becomes further removed against subsequent sulphonation of the benzene rings of the amines (II), originally formed in the ' normal ' course of the Schmidt reaction. However, direct inductive effects at this distance are generally very small.

EXPERIMENTAL

M.p.s were determined with a Fisher–Johns apparatus. I.r. spectra were recorded with a Perkin-Elmer 21 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Schmidt Reaction of γ-Phenylbutyric Acid (I).—(a) *With sulphuric acid.* Sodium azide (3·64 g, 0·056 mol) was added in five portions during 30 min to a vigorously stirred suspension of γ-phenylbutyric acid[9] (8·2 g, 0·05 mol) in concentrated sulphuric acid (20 ml) and chloroform (80 ml), preheated to 40°C. After 1 h at 40°C, the mixture was cooled to 0°C and poured on ice; the precipitate (4·4 g, 40%) was filtered off and gave leaflets of 4-(3-*aminopropyl*)-*benzenesulphonic acid* (III), decomp. >350° (from dilute hydrochloric acid), $\nu_{max.}$ (KBr) 3280, 3075, 1650, 1475, 1190, 1170, 1040, 1010, 850, and 795 cm^{-1} (Found: C, 50·5; H, 6·2; N, 6·3; S, 14·7. $C_9H_{13}NO_3S$ requires C, 50·2; H, 6·0; N, 6·5; S, 14·9%).

The chloroform layer was separated from the filtrate and the aqueous phase was extracted with chloroform (2 × 30 ml). The combined extracts were washed until neutral with 10% sodium carbonate solution, dried (Na_2SO_4), and evaporated, leaving almost pure 4,5-dihydro-1*H*-1-benzazepin-2(3*H*)-one (4 g., 50%), m.p. 140—141° (from benzene), identical with an authentic sample.[5]

(b) *With polyphosphoric acid.* Sodium azide (3 g, 0·046 mol) and γ-phenylbutyric acid (5 g, 0·03 mol) were added simultaneously with stirring during 30 min to a solution of phosphorus pentoxide in 85% phosphoric acid (2 : 1 w/w; 75 g) at 80—85°C. After 2 h more at this temperature, the mixture was poured into cold water (350 ml) and extracted twice with ether. The extracts were washed with 5% hydrochloric acid, dried (Na_2SO_4), and evaporated, leaving pure benzazepinone (IX), m.p. 140—141° (2 g, 40%), identical with an authentic specimen.[5] The aqueous layer was basified with concentrated ammonia and the liberated amine (II) was taken up in ether and dried (Na_2SO_4). Evaporation of the solvent gave the amine (1 g, 24%), identified as its benzoyl derivative, m.p. 60° (lit.,[10] 60°).

N-Benzoyl-3-(4-benzoyloxyphenyl)propylamine (VI).—The amino-sulphonic acid (III) (1 g) was fused with solid potassium hydroxide (0·25 g) and the melt was dissolved in water (3 ml). Without isolation of the aminophenol

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[8] H. R. Snyder and F. X. Werber, *Org. Synth*, 1967, Coll. Vol. III, 798.

[9] W. Reppe, *Annalen*, 1955, **596**, 177.

[10] K. Kindler, B. Hedemann, and E. Schärfe, *Annalen*, 1948, **560**, 220.

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formed, the alkaline solution was subjected to Schotten-Baumann benzoylation. The precipitated dibenzoyl derivative (VI) (1·2 g, 72%) yielded needles, m.p. 128° (from ethanol). An identical product was obtained when a solution of 3-(4-hydroxyphenyl)propylamine hydriodide [3] (1 g) in 10% sodium hydroxide (20 ml) was shaken vigorously with benzoyl chloride (2 ml). The *product* (1·2 g, 92%) was washed with water, and recrystallised from ethanol; m.p. 128° (Found: C, 76·8; H, 5·9; N, 3·8. $C_{23}H_{21}NO_3$ requires C, 76·9; H, 5·9; N, 3·9%).

p-*Chlorosulphonylbenzoic Acid* (V).—A solution of the amino-sulphonic acid (III) (2·15 g) and potassium permanganate (5 g) in water (150 ml) was heated with stirring at 70—80°C for 3 h with occasional addition of 10% potassium hydroxide to keep the mixture strongly alkaline. Excess of permanganate was then destroyed with ethanol, and the manganese dioxide was filtered off. The filtrate was extracted with ether, acidified with hydrochloric acid, and evaporated to dryness. Crystallisation of the residue from the minimum amount of water provided the potassium salt of (IV) (2·2 g, 92%). It was dried (P_2O_5) and converted [4] into *p*-chlorosulphonylbenzoic acid (1·8 g), m.p. and mixed m.p. 232—235°.

Schmidt Reaction of δ-Phenylvaleric Acid (X).—The reaction of δ-phenylvaleric acid (X) [11] (4·45 g, 0·025 mol) and sodium azide (1·95 g, 0·03 mol) with concentrated sulphuric acid (10 ml) and chloroform (40 ml), as described for (I), yielded 4-(4-*aminobutyl*)*benzenesulphonic acid* (4·8 g, 80%) (XI). No neutral or basic products could be isolated. The acid was obtained as needles, decomp. >350° (from water), $\nu_{max.}$ (KBr) 3280, 3075, 1650, 1475, 1210, 1160, 1110, 1025, 1000, 880, 815, and 765 cm^{-1} (Found: C, 52·6; H, 6·6; N, 6·1; S, 13·9. $C_{10}H_{15}NO_3S$ requires C, 52·4; H, 6·6; N, 6·1; S, 14·0%).

Oxidation to the carboxylic acid (IV) and conversion into the sulphonyl chloride (V) was carried out as described for (III).

Financial support by the National Institutes of Health, National Cancer Institute is gratefully acknowledged.

[0/214 *Received, February 9th,* 1970]

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