444. *Azabenzocycloheptenones. Part II.* Dieckmann Cyclisation of Arylamino-esters.*

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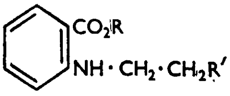
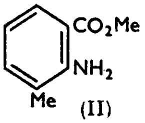
Attempted acyloin reduction of the diester (I; $R = Me$, $R' = CO_2Me$) gave the quinolone (III; $R = CO_2Me$). Dieckmann cyclisation of the diester (IV; $R = p\text{-}C_6H_4Me{\cdot}SO_2$) yielded the azabenzo*cyclo*heptenone (V).

As the synthesis of azabenzo*cyclo*heptenones by Friedel–Crafts cyclisation is not practicable (see Part I *) alternative routes based on anthranilic acid derivatives have been explored. Cyanoethylation of anthranilic acid using acid catalysts [1] was unsuccessful but the nitrile (I; $R = H$, $R' = CN$) was readily obtained in the presence of potassium hydroxide. Hydrolysis then gave the diacid (I; $R = H$, $R' = CO_2H$) from which both the mono- (I; $R = H$; $R' = CO_2Me$) and the di-methyl ester were obtained by the Fischer–Speier method. During attempts to obtain the diester directly from the nitrile (I; $R = H$; $R' = CN$) it was found that prolonged reaction with methanolic sulphuric acid gave, in addition, a primary amine, regarded as (II) or a mixture of (II) and its isomer methyl 2-amino-5-methylbenzoate. This would arise by a β-elimination of acrylonitrile followed (or preceded) by *N*-methylation and *N* ⟶ *C* migration of the methyl group. The original intention was to cyclise the diester (I; $R = Me$; $R' = CO_2Me$) to an acyloin but in practice none of the seven-membered ring compound was obtained, the chief product being the keto-ester (III; $R = CO_2Me$) along with a little of the quinoline (III; $R = H$). A series of cyclic aza-acyloins has been made by Leonard and his co-workers [2] who found that cyclic aza-keto-esters were often formed at the same time and a seven-membered cyclic acyloin could only be obtained in 10% yield. We also prepared the quinoline (III; $R = CO_2Me$) under Dieckmann conditions but the yield was low, probably owing to the presence of a free NH group in the starting material. So we turned to the higher homologue (IV). The *N*-toluene-*p*-sulphonyl derivative (used to avoid lactam formation) was obtained by condensing methyl *N*-toluene-*p*-sulphonylanthranilate with ethyl γ-bromobutyrate, and when subjected to the Dieckmann reaction yielded, after hydrolysis, the azabenzo*cyclo*heptenone (V). The yield was again low and the crude product contained much starting material.



(I)



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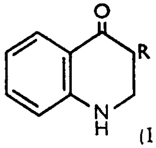

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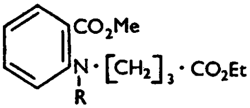

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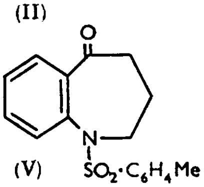

(V)

Experimental

N-2′-*Cyanoethylanthranilic Acid.*—Anthranilic acid (137 g.) was refluxed with acrylonitrile (53 g.), 40% aqueous potassium hydroxide (20 ml.), and ethanol (50 ml.) for 18 hr., then the solution was poured into cold water (2 l.), stirred, and adjusted to pH 5 with hydrochloric acid. The precipitated *acid* was collected and washed with cold water; it crystallised from ethanol (500 ml.)–water (400 ml.) in needles, m. p. 169° (127 g., 67%) (Found: C, 62·9; H, 5·35; N, 14·9. $C_{10}H_{10}O_2N_2$ requires C, 63·15; H, 5·3; N, 14·75%).

N-2′-*Carboxyethylanthranilic Acid.*—The above acid (40 g.) was refluxed with 20% aqueous

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* Part I, preceding paper.

[1] Braunholz and Mann, *J.*, 1949, 67; 1952, 3046; 1953, 1817.

[2] Leonard, Fox, and Oki, *J. Amer. Chem. Soc.*, 1954, **76**, 5708.

potassium hydroxide (1 l.) until ammonia was no longer evolved. The cooled solution was filtered and neutralised with hydrochloric acid, and the precipitate collected and washed with cold water. The *diacid* crystallised from water in needles, m. p. 182° (95%) (Found: C, 57·65; H, 5·25; N, 7·0. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3; N, 6·7%). The N-*toluene*-p-*sulphonyl derivative* crystallised from aqueous methanol in needles, m. p. 188—189° (Found: C, 56·05; H, 4·6; N, 4·05; S, 8·75. $C_{17}H_{17}O_6NS$ requires C, 56·15; H, 4·7; N, 3·85; S, 8·8%). The *dimethyl ester* was obtained by refluxing the acid (46 g.) in dry methanol (500 ml.) while dry hydrogen chloride was passed into the solution. After 12 hr., the mixture was cooled to 0° and poured into a stirred 20% solution of sodium hydroxide (750 ml.) at $<10°$. After 15 hr. at 0°, the product was collected, washed with iced water, dried *in vacuo*, and crystallised from light petroleum (b. p. 40—60°), forming prisms, m. p. 36° (26·5 g.; 65% based on the acid consumed) (Found: C, 60·95; H, 6·35; N, 5·75. $C_{13}H_{15}O_4N$ requires C, 60·75; H, 6·35; N, 5·9%). Starting material (12 g.) was recovered. In one experiment when hydrogen chloride was passed for only 50 min., extraction of the neutral solution with chloroform gave a *monomethyl ester* which crystallised from light petroleum (b. p. 100—120°) in needles, m. p. 101° (Found: C, 59·15; H, 5·95; N, 6·25. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·85; N, 6·3%): it was soluble in cold sodium carbonate solution and gave a violet ferric chloride colour like the parent acid and nitrile (above). This is consistent with structure (I; $R = H$, $R' = CO_2Me$) as the diester gave no colour. The diester gave a *monoester monoamide* which separated from light petroleum (b. p. 100—120°) in needles, m. p. 105° (Found: C, 59·2; H, 6·2; N, 12·7. $C_{11}H_{14}O_3N_2$ requires C, 59·45; H, 6·35; N, 12·6%).

Methyl 2-*Amino*-3-*methylbenzoate*.—*N*-2′-Cyanoethylanthranilic acid (230 g.) was heated on a steam-bath for 43 hr. with dry methanol (208 ml.) and concentrated sulphuric acid (136 ml.). The mixture was poured into cold water, made alkaline with sodium carbonate, and extracted with chloroform. The dried extract was evaporated and the bulk of the residue distilled at 180—190°/10 mm. Redistillation gave the diester as principal fraction, b. p. 186°/10 mm., m. p. 36°. The remainder, which did not solidify, was fractionated through a 25 cm. column and collected at 83°/0·05 mm. (Found: C, 65·6; H, 6·6; N, 9·1. Calc. for $C_9H_{11}O_2N$: C, 65·45; H, 6·65; N, 8·5%). Hydrolysis gave the amino-acid, m. p. 163·5° (from light petroleum, b. p. 100—120°) (Found: N, 9·45. Calc. for $C_8H_9O_2N$: N, 9·25%). The *hydrochloride* crystallised from anisole in needles, m. p. 175·5° (Found: Cl, 18·9. $C_8H_{10}O_2NCl$ requires Cl, 18·95%) (cf. lit., 2-amino-3-methylbenzoic acid, m. p. 168—169°[3] or 172°[4]; methyl ester, b. p. 153°/23 mm.[3]: 2-amino-5-methylbenzoic acid, m. p. 172°[5], 175°[4], or 177°[6]; methyl ester, m. p. 62°). The amino-ester (b. p. 83°/0·05 mm.) was diazotised and coupled with β-naphthol, giving an *azo-derivative* which separated from acetic acid or ethanol in red needles, m. p. 179° (Found: N, 9·05. $C_{18}H_{14}O_3N_2$ requires N, 9·15%).

1 : 2 : 3 : 4-*Tetrahydro*-3-*methoxycarbonyl*-4-*quinolone*.—(*a*) Methyl *N*-2′-methoxycarbonylethylanthranilate (9·25 g.) was refluxed for 22 hr. in sodium-dried benzene (75 ml.) containing finely dispersed sodium (1·2 g.) and ethanol (0·5 ml.). The mixture was then cooled, shaken with ice, and neutralised with hydrochloric acid. The benzene layer was separated and the aqueous layer extracted with chloroform. The combined organic solutions were dried and evaporated, and the *product* sublimed *in vacuo*. The sublimate separated from light petroleum (b. p. 100—120°) in yellowish-green crystals, m. p. 113° (0·47 g.) (Found: C, 64·4; H, 5·25; N, 6·6. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·35; N, 6·85%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate–light petroleum (b. p. 80—90°) in dark red needles, m. p. 221° (Found: C, 52·9; H, 4·2. $C_{17}H_{15}O_6N_5$ requires C, 53·0; H, 3·9%). The ON-*ditoluene*-p-*sulphonyl derivative* was prepared in pyridine, and crystallised from ethanol in needles, m. p. 136—137° (Found: C, 58·3; H, 3·95; N, 2·5; S, 11·95. $C_{25}H_{23}O_7NS_2$ requires C, 58·45; H, 4·5; N, 2·7; S, 12·45%). The residue after sublimation was a yellow oil which gave a 2 : 4-dinitrophenylhydrazone, m. p. 260° (from glacial acetic acid), not depressed on admixture with the 2 : 4-dinitrophenylhydrazone of 1 : 2 : 3 : 4-tetrahydro-4-quinolone.[7] Hydrochloric acid hydrolysis of the keto-ester, m. p. 113°, also gave a yellow oil which formed a 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 260° (Found: C, 54·9; H, 4·0; N, 21·0. Calc. for $C_{15}H_{13}O_4N_5$: C, 55·05; H, 4·0; N, 21·4%).

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[3] Freundler, *Bull. Soc. chim. France*, 1907, **1**, 222.
[4] Findeklee, *Ber.*, 1905, **38**, 3553.
[5] Panaotović, *J. prakt. Chem.*, 1886, **33**, 63, 69.
[6] Anschütz and Schultz, *Ber.*, 1925, **58**, 65.
[7] Johnson, Woroch, and Buell, *J. Amer. Chem. Soc.*, 1949, **71**, 1903.

(*b*) Methyl *N*-2′-methoxycarbonylethylanthranilate (10 g.) was dissolved in sodium-dried xylene (400 ml.) and added from a capillary to a suspension of finely divided sodium (5 g.) in boiling sodium-dried xylene (200 ml.) vigorously stirred under oxygen-free nitrogen in a creased * flask. Stirring was continued for ½ hr. after the addition was complete (8½ hr.), and after cooling, glacial acetic acid (15 g.) was added, followed by water (200 ml.), The mixture was made alkaline (pH 10) with sodium carbonate, the xylene layer was removed, and the aqueous layer was extracted with chloroform. The combined organic solutions were dried and evaporated, leaving an oil which distilled at 145°/0·05 mm. (0·5 g.). It was identified as the parent quinolone by its 2 : 4-dinitrophenylhydrazone, m. p. 260°. The solid residue was sublimed at 160°/0·05 mm. (4·2 g., 48%). Crystallised from light petroleum (b. p. 100—120°) it had m. p. 113°, undepressed on admixture with material prepared as in (*a*).

Methyl N-*Toluene*-p-*sulphonylanthranilate*.—Methyl anthranilate (50 g.) was treated with toluene-*p*-sulphonyl chloride (80 g.) in dry pyridine (160 ml.) and the product crystallised from methanol in prisms, m. p. 113° (92 g., 91%).

Ethyl γ-N-(2-*Methoxycarbonylphenyl*)-N-*toluene*-p-*sulphonamidobutyrate*.—The preceding ester (75 g.), ethyl γ-bromobutyrate (48 g.), anhydrous potassium carbonate (90 g.), and dry acetone (200 ml.) were refluxed together for 24 hr., cooled, poured into water (1 l.), and left for several hr., with stirring and cooling. The precipitate was filtered off, dried at 50°, and crystallised from ethyl acetate–light petroleum (b. p. 80—90°) in needles, m. p. 102—103° (89 g., 86%) (Found: C, 60·2; H, 5·9; N, 3·35; S, 7·15. $C_{21}H_{25}O_6NS$ requires C, 60·1; H, 6·0; N, 3·35; S, 7·65%). Hydrolysis of the *ester* with aqueous 2N-sodium hydroxide gave a *diacid* which separated from aqueous ethanol in needles, m. p. 229—231° (Found: C, 57·4; H, 4·8; N, 4·0. $C_{18}H_{19}O_6NS$ requires C, 57·3; H, 5·05; N, 3·7%).

3-*Toluene*-p-*sulphonyl*-3-*azabenzo*cyclo*hepten*-7-*one*.—Potassium (2 g.) was dispersed in boiling sodium-dried benzene (200 ml.) stirred in a creased flask with a mechanical paddle and a nitrogen inlet. Dry oxygen-free nitrogen was passed into the flask while *tert*.-butyl alcohol (5·5 ml.) was cautiously added and washed into the solution with dry benzene. To this stirred, refluxing solution, a solution of the preceding diester (20 g.) in benzene (200 ml.) was added during 2 hr., an atmosphere of nitrogen being maintained. After being stirred and refluxed for 20 hr., the mixture was cooled and neutralised with dilute hydrochloric acid. The benzene layer was dried and evaporated, leaving a residue (18 g.) which contained starting material. (In one experiment 11 g. of the original ester were obtained by repeated crystallisation.) This residue was refluxed with alcohol (90 ml.) and concentrated hydrochloric acid (50 ml.) for 1½ hr., cooled, diluted with water (600 ml.), and extracted with chloroform. The extract was dried and evaporated, leaving an oil which gave a positive test with Brady's reagent. It was purified either by refluxing it with aqueous sodium hydroxide for ½ hr. or *via* its 2 : 4-dinitrophenylhydrazone. Pure ketone was obtained from the latter by the following modification of Rupe and Gassmann's procedure.[8] The 2 : 4-dinitrophenylhydrazone (4 g.), *m*-nitrobenzaldehyde (1·22 g.), *n*-butyl alcohol (100 ml.), and concentrated hydrochloric acid (2·0 ml.) were refluxed gently for 40 hr. and cooled to 10°. The mixture was filtered and the residue washed with methanol. The combined filtrate and washings were evaporated in a vacuum, leaving a product which crystallised from light petroleum (b. p. 100—120°) in needles, m. p. 126°, alone or mixed with the *ketone* obtained by alkaline hydrolysis (1·82 g.) (Found: C, 64·5; H, 5·6; N, 4·05. $C_{17}H_{17}O_3NS$ requires C, 64·7; H, 5·45; N, 4·45%). The infrared spectrum shows $\lambda_{C=O}$ 1688 cm.$^{-1}$ in CCl_4. Variation of the Dieckmann conditions failed to improve the yield. The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid–ethanol or nitrobenzene as yellow needles, m. p. 236°. It was identical with the material obtained from the crude reaction product (Found: C, 55·7; H, 4·35; N, 14·2. $C_{23}H_{21}O_6N_5S$ requires C, 55·75; H, 4·25; N, 14·15%). The p-*nitrobenzylidene derivative* crystallised from glacial acetic acid in needles, m. p. 249—250° (Found: C, 63·95; H, 4·7; N, 5·95; S, 7·1. $C_{24}H_{20}O_5N_2S$ requires C, 64·25; H, 4·5; N, 6·25; S, 7·15%).

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* *I.e.*, a flask in which indentations were made whilst hot.

[8] Rupe and Gassmann, *Helv. Chim. Acta*, 1936, **19**, 569.