

**539.** *The Schmidt Reaction with Unsymmetrical Ketones.*

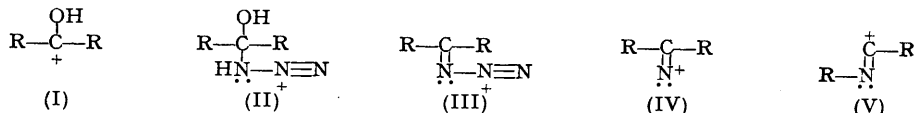
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The Schmidt reaction with a number of unsymmetrical ketones has been examined. Two types of product are formed:  $\text{CORR}' \longrightarrow \text{R}'\text{CO}\cdot\text{NHR}$  and/or  $\text{R}\cdot\text{CO}\cdot\text{NHR}'$ .

The factors governing the course of the reaction are discussed.

IN connection with a scheme to examine the relation between polynuclear heterocyclic systems and their carbocyclic analogues (Badger *et al.*, *J.*, 1951, 3199, 3204, 3207, 3211), the study of various synthetic methods has been undertaken. One such method involves the treatment of cyclic carbonyl compounds with hydrazoic acid (for a review of the Schmidt reaction see Wolff, "Organic Reactions," 1946, Vol. 3, pp. 307—336), and the use of polynuclear *o*-quinones for this purpose seemed worthy of further investigation (cf. Caronna, *Gazzetta*, 1941, **71**, 481; *Chem. Abs.*, 1943, **37**, 118; Stephenson, *J.*, 1949, 2620). "Unsymmetrical" *o*-quinones, such as chrysaquinone, can conceivably lead to two different products, and the available literature on the Schmidt reaction provides little or no information as to which structure is likely to be formed predominantly. This problem is at present under investigation, but as a preliminary to the studies with *o*-quinones, the effect of hydrazoic acid on some unsymmetrical ketones has been investigated, and the results are reported here. While this work was in progress several important contributions to the study of the Schmidt reaction with unsymmetrical ketones were published by Smith and his co-workers (*J. Amer. Chem. Soc.*, 1948, **70**, 320; 1950, **72**, 2503, 3718).

According to the accepted mechanism of the Schmidt reaction (Smith, *loc. cit.*; Newman and Gildenhorn, *ibid.*, 1948, **70**, 317), the carbonyl compound is first converted into a carbonium ion (I) which then reacts with hydrazoic acid to give (II). Subsequent elimination of water gives the intermediate (III), which loses nitrogen to give (IV), and this rearranges to the ion (V). On addition of water, (V) is converted into the acid amide, R·CO·NHR.



The structure of the hypothetical intermediate (III) resembles that of a ketoxime, and its rearrangement into the ion (V) is entirely analogous to the Beckmann transformation of ketoximes. Indeed, both reactions proceed through the common intermediate (IV).

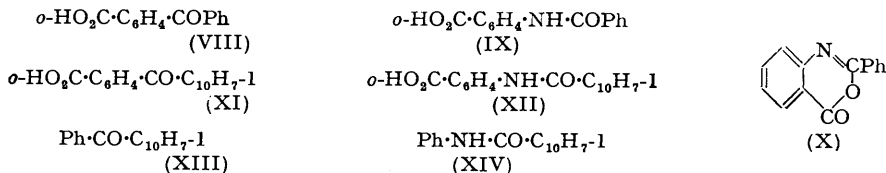
If an unsymmetrical ketone is used, the intermediate (III) should be capable of existing in geometrical isomerides of the types (VI) and (VII), and two acid amides, R·CO·NHR' and R'·CO·NHR, might be expected from the Schmidt reaction, depending on whether R or R' migrates from C to N.



Smith (*loc. cit.*) has already shown that "migratory aptitudes" are unimportant in the Schmidt reaction. If, therefore, the *trans*-group (R in VI; R' in VII) migrates (as it does in the Beckmann rearrangement), then the ratio of the *syn*- and the *anti*-configuration in the intermediate should determine the ratio of the amides produced. The problem therefore becomes one of determining the factors which influence the ratio of the isomerides (VI) and (VII) in the intermediate.

Steric factors are certainly of importance here and, other things being equal, the more stable isomeride would be that in which the azo-group is orientated away from the bulkier, or *ortho*-substituted, group R. It is to be expected, therefore, that the Schmidt reaction will take place predominantly by migration of the bulkier group.

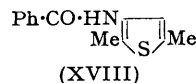
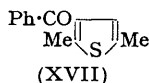
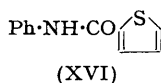
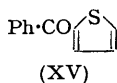
In agreement with this conclusion, it has been found that the Schmidt reaction with *o*-benzoylbenzoic acid (VIII) takes place exclusively, or almost exclusively, by migration of the carboxyphenyl radical. *N*-Benzoylanthranilic acid (IX) was isolated in almost quantitative yield as the free acid or the anhydride (X) (a preliminary account of this experiment has already been published: Badger and Howard, *Chem. and Ind.*, 1950, 601). With *o*-1-naphthoylbenzoic acid (XI), the main product was found to be *N*-1-naphthoylanthranilic acid (XII), also formed by migration of the carboxyphenyl radical. On the other hand, in the Schmidt reaction with 1-benzoylnaphthalene (XIII) there was



predominant migration of the phenyl (or *less* bulky) group, the chief product being  $\alpha$ -naphthanilide (XIV). It is also of interest that the related compounds, 2-methylbenzophenone and 1-benzoylphenanthrene, undergo the reaction by preferential migration of the phenyl group (Smith, *loc. cit.*; Dice and Smith, *J. Org. Chem.*, 1949, **14**, 179). However, 9-benzoylanthracene and benzoylmesitylene could not be induced to react with hydrazoic acid.

In the case of 2-benzoylthiophen (XV) there can be little or no difference in the steric effects of the two aryl groups; but in this case also the reaction appeared to take place predominantly by migration of the phenyl group. The only product which could be

isolated was thiophen-2-carboxyanilide (XVI). With 3-benzoyl-2:5-dimethylthiophen (XVII), however, the steric effect may again be operative, for the major product was found to be 3-benzamido-2:5-dimethylthiophen (XVIII).



The results so far, therefore, indicate that the bulkier group does normally migrate from C to N, but that there are several exceptions. It seems that the configuration of the intermediate (III) is not determined *solely* by the steric environment of the carbonyl group.

#### EXPERIMENTAL

*Schmidt Reactions.*—(i) *Method A.* A mixture of the ketone (0.02 mol.), chloroform (100 c.c.), and concentrated sulphuric acid (20 c.c.) was warmed to 50°. Sodium azide (0.04 mol.) was then added gradually, with stirring, during 1 hour. Stirring was continued for a further 3 hours, after which the mixture was poured into cold water. The chloroform layer was separated and the aqueous layer extracted with chloroform. The combined chloroform solutions were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated at room temperature, to give the crude product.

(ii) *Method B.* A solution of the ketone (0.02 mol.) in trichloroacetic acid (40 g.) was warmed to 50°. Sodium azide (0.04 mol.) was then added gradually, with stirring, during 1 hour and concentrated sulphuric acid (15 c.c.) was added gradually during the addition of sodium azide. Stirring was continued for a further 1½—3 hours. The mixture was then added to water and, after being kept overnight in the refrigerator, the crude product was collected by filtration.

*o-Benzoylbenzoic Acid.*—(a) The crude product obtained by method *A* was separated into neutral and acidic fractions with cold dilute sodium carbonate solution. The acid fraction, obtained in 31% yield, crystallised from aqueous ethanol in colourless needles, m. p. 179°, and was identified as *N*-benzoylanthranilic acid by direct comparison with an authentic specimen prepared by benzoylation of anthranilic acid (Brückner, *Annalen*, 1880, 205, 130). The neutral fraction, obtained in 67% yield, crystallised from benzene in fine colourless needles, m. p. 123°. It was identified as anhydro-*N*-benzoylanthranilic acid by analysis (Found: C, 75.6; H, 4.2. Calc. for  $\text{C}_{14}\text{H}_9\text{O}_2\text{N}$ : C, 75.3; H, 4.0%) and by mixed m. p. with an authentic specimen (Heller and Fiesselmann, *ibid.*, 1902, 324, 134).

(b) The crude product obtained in 90.5% yield by method *B* was shown to be substantially pure *N*-benzoylanthranilic acid by direct comparison with an authentic specimen.

*o-1-Naphthoylbenzoic Acid.*—(i) The crude product obtained (in 30% yield) by method *A* was shown to be substantially pure anhydro-*N*-1-naphthoylanthranilic acid. After recrystallisation from ethanol, it formed pale yellow needles, m. p. 134° (Found: C, 79.1; H, 3.9.  $\text{C}_{18}\text{H}_{11}\text{O}_2\text{N}$  requires C, 79.1; H, 4.1%). The m. p. was not depressed by admixture with a specimen prepared from 1-naphthoyl chloride and anthranilic acid.

Hydrolysis of the anhydro-compound with boiling sodium carbonate solution followed by precipitation with hydrochloric acid gave the free acid. After recrystallisation from ethanol, *N*-1-naphthoylanthranilic acid formed colourless needles, m. p. 235° (Found: C, 74.3; H, 4.6.  $\text{C}_{18}\text{H}_{13}\text{O}_3\text{N}$  requires C, 74.2; H, 4.5%).

(ii) The crude product obtained by method *B* was dissolved in dilute aqueous sodium hydroxide and reprecipitated with hydrochloric acid. The resulting acid (m. p. 200—220°) was obtained in 45% yield. After one recrystallisation from ethanol, it had m. p. 230—233°, not depressed by admixture with the previous specimen.

*1-Benzoylnaphthalene.*—(a) Numerous attempts to carry out the Schmidt reaction with this substance by method *A*, or by slight modifications of it, were unsuccessful. The ketone was always recovered unchanged.

(b) By method *B*, however, reaction proceeded readily, and a crude product was obtained in almost quantitative yield. Fractional crystallisation from ethanol gave  $\alpha$ -naphthanilide, m. p. 153—159°, in 64% yield, and no pure product could be isolated from the oily material recovered from the liquors. After further purification, the  $\alpha$ -naphthanilide formed colourless plates, m. p. 162—163° (Gibson *et al.*, *J.*, 1926, 2259, give m. p. 162—163°) not depressed on admixture with an authentic specimen prepared from 1-naphthoyl chloride and aniline. Admixture with the isomeric substance, *N*-benzoyl-1-naphthylamine, m. p. 161—162°, however, gave a substantial depression.

**9-Benzoylanthracene.**—This was prepared by a Friedel-Crafts reaction between anthracene and benzoyl chloride, as described in *Org. Synth.*, **30**, 1, for the preparation of 9-acetylanthracene. Attempts to carry out the Schmidt reaction with this ketone under a variety of different experimental conditions were all unsuccessful, the ketone being recovered unchanged.

**Benzoylmesitylene.**—This was prepared similarly from mesitylene and benzoyl chloride. It was recovered unchanged in all attempts to carry out the Schmidt reaction.

**2-Benzoylthiophen.**—The crude product obtained by method *B* was decolorised in acetone solution with charcoal and after one recrystallisation from alcohol gave thiophen-2-carboxyanilide, m. p. 140—145°, in 49% yield. No pure product could be obtained from the liquors. The pure anilide was obtained by sublimation at 150°/0.2 mm., followed by further recrystallisation from alcohol, and formed colourless needles, m. p. 144—145° (Found: C, 65.2; H, 4.65. Calc. for  $C_{11}H_9ONS$ : C, 65.0; H, 4.5%). Leuckart and Schmidt (*Ber.*, 1885, **18**, 2338) give m. p. 140°. The m. p. was not depressed on admixture with a specimen, m. p. 144—145°, prepared from thiophen-2-carboxy chloride and aniline.

**3-Benzoyl-2:5-dimethylthiophen.**—The Schmidt reaction with 3-benzoyl-2:5-dimethylthiophen (Buu-Hoï and Hoán, *Rec. Trav. chim.*, 1948, **67**, 309) was carried out according to method *B* but at 35—40°. The resulting sticky solid was recrystallised from light petroleum (b. p. 40—70°) from which the product, m. p. 157—162°, separated in 58% yield. After further recrystallisation, 3-benzamido-2:5-dimethylthiophen was obtained as long colourless needles, m. p. 164—165° (Found: C, 67.5; H, 5.6.  $C_{13}H_{13}ONS$  requires C, 67.5; H, 5.6%).

Benzamidodimethylthiophen was also prepared as follows. 2:5-Dimethylthiophen-3-carboxylic acid (Steinkopf *et al.*, *Annalen*, 1938, **536**, 128), in trichloroacetic acid and a little sulphuric acid, was treated with sodium azide in the usual way. The resulting amine was benzoylated with benzoyl chloride and sodium hydroxide, to give (after recrystallisation from light petroleum) the benzamido-compound, m. p. 164—165°, not depressed on admixture with a specimen prepared as above.

The m. p. of the benzamidodimethylthiophen prepared from benzoyldimethylthiophen was, however, depressed by admixture with the isomeric substance, 2:5-dimethylthiophen-3-carboxyanilide (see below).

**2:5-Dimethylthiophen-3-carboxyanilide.**—2:5-Dimethylthiophen-3-carboxylic acid was converted by thionyl chloride and then aniline into the *anilide* which crystallised from light petroleum (b. p. 40—70°) in colourless needles, m. p. 139.5—140° (Found: C, 67.8; H, 5.9.  $C_{13}H_{13}ONS$  requires C, 67.5; H, 5.7%).

Microanalyses were carried out by the C.S.I.R.O. Microanalytical Laboratory, Melbourne.

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