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ON THE MECHANISM OF CARBOXYL CONDENSATIONS BY CARBODIIMIDES

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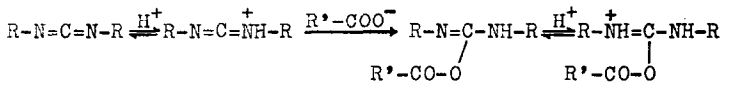
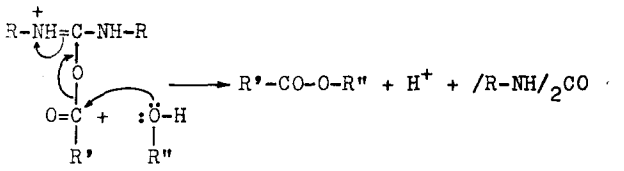
A well known important method for the preparation of carboxylic derivatives consists in the condensation of carboxylic acids with nucleophyles in the presence of carbodiimides, eg.dicyclohexyl-carbodiimide. This method has frequently been applied for the synthesis of anhydrides, amides /inter al. peptides/ and esters.

For these reactions the following four step mechanism, represented for the condensation with alcohols, has been suggested by Khorana and coworkers [1] :



I



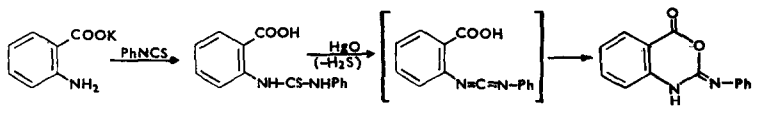
[1] M. Smith, J.G. Moffat and H.G. Khorana: J.A.C.S. 80, 6204 /1958/

Although this mechanism seems reasonably in every respect, it has in fact never been proved. Notably, the postulated O-acyl-isourea intermediate /I/ has never been isolated and, therefore, its reactions with nucleophyles could not have been investigated.

We now have succeeded in synthesising a cyclic O-acyl--isourea by intramolecular condensation of an /o-carboxy--phenyl/-carbodiimide /III/ and thus had the opportunity to examine its reactions with different nucleophyles, thereby proving the mechanism outlined above.

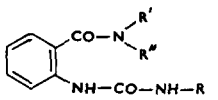
Potassium anthranilate has been subjected to reaction with phenyl-isothiocyanate to form o-phenylthioureidobenzoic acid /II, mp.: about 280° with slight dec. from 160° x; found C 61,40 H 4,46 S 11,61 and 11,76; $C_{14}H_{12}N_2O_2S$ = 272,3 requires C 61,76 H 4,44 S 11,76/. This, on treatment with mercuric oxide in acetone readily loses one mole of hydrogen sulfide yielding thereby, instead of the expected 2-carboxy-diphenyl-carbodiimide /III/, by cyclisation of the latter, 2/1H/-phenylimino--3,1,4H-benzoxazin-4-one /IV; mp.: 192-193°, from benzene; found C 70,67 and 70,74 H 4,27 and 4,22 N 11,95 and 11,95; $C_{14}H_{10}N_2O_2$ = 238,2 requires C 70,58 H 4,23 N 11,76/.

x II readily cyclises to 3-phenyl-2-thio-2,4/1H,3H/-quinazolinedione; the two compounds may be separated by treating their alcaline solution first with carbon dioxide and then with hydrochloric acid at 0°; IV may be purified by treating its cold acetonic solution with petrolether.



II III IV

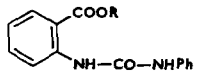
(IVa = IV with H instead of Ph)



V

a. R = H
R' = Me, Et, Ph, $PhCH_2$, CH_2COOEt
R'' = H or R' = R'' = Et

b. R = Ph, R' = $PhCH_2$, R'' = H



VI

a. R = H
b. R = Me

The structure of the latter compound has been proved by its IR spectrum, the more important bands being at 1750/cm /carbonyl/, 3300, 1610 and 505/cm /imino group/, 1650/cm /exocyclic C=N bond/, 1585 and 1480/cm /benzene ring/ and 758/cm /o-disubstituted benzene/. Recently an analoge of IV, 2/1H/-imino-3,1,4H-benzoxazin-4-one, IVa, as well as its hydrochloride have been synthesised too [2].

Te reaction of IVa and its hydrochloride with alcohols, leading to o-ureido-benzoic esters has already been described [2]. Attention should be called to the fact that the

[2] K. Lempert and G. Doleschall: Tetrahedron Letters 1963, No. 12, 781.

hydrochloride has been found to react clearly more readily than the free base [2], thus proving the susceptibility of these reactions towards acid catalysis, as it has been postulated by Khorana [1].

IVa reacts readily with amines and amino esters too, yielding the corresponding o-ureido-benzamides Va [3]. With aniline the hydrochloride of IVa gives the same product as the base; with benzylamine, however, the hydrochloride yields, obviously as a consequence of consecutive, e.g. cyclisation reactions caused by the acid present, complex mixtures difficult to separate.

IV - in contrast to IVa - does not react under similar conditions with alcohols. However the hydrochloride of IV /mp.: 265-270° with slight decomposition from 170°/, prepared by passing dry hydrogen chloride into a solution of the base in a benzene ether mixture, yields, on refluxing with water or methanol, o-phenylureido-benzoic acid /VIa, mp. and mixed mp. with an authentic sample prepared from anthranilic acid and phenyl-isocyanate: 183-184°, from aqueous alcohol; lit. [4]: 181°/ and its methyl ester /VIb, mp., mixed mp. with an authentic sample prepared from methyl anthranilate and phenyl-isocyanate and lit.-mp.[5]:

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[3] K. Lempert and G. Doleschall: unpublished

[4] C. Paal: Ber. 27, 978 /1894/

[5] P. Grammaticakis: Compt.rend. 247, 2013 /1958/

143-144°, from ligroin/, respectively, thus demonstrating again the susceptibility of the reactions under discussion towards acid catalysis. IVa, under these conditions, yields, evidently by cyclisation of the o-ureido-benzoic acid and its esters primarily formed, 2,4/1H,3H/-quinazolinedione [2]. That an analogous cyclisation does not take place with VIa and b is certainly a consequence of the reduced nucleophylity of the nitrogen bearing the phenyl group.

Treatment of IV with benzylamine in dry dioxane either at room temperature or under reflux leads to N-benzyl-/o-phenyl-ureido-benzamide/ /Vb, mp.: 194-195° from 50% aqueous dioxane; found C 73,31 H 5,24; $C_{21}H_{19}N_3O_2$ = = 345,4 requires C 73,02 H 5,55/.