SYNTHESIS AND REACTIVITY OF HETEROCYCLIC α-DIAZO CARBONYL COMPOUNDS+

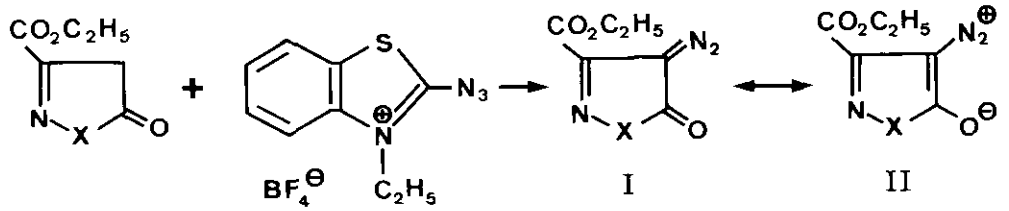
Axel Schmitz[1], Udo Kraatz and Friedhelm Korte*
Institut für Chemie der Technischen Universität München
and Institut für Ökologische Chemie der Gesellschaft für
Strahlen- und Umweltforschung mbH München
D - 8050 Freising-Weihenstephan, Am Löwentor

Synthesis of α-diazo substituted 3-carboxylic esters of isoxazolone and pyrazolone (3 a, b) by diazo group transfer succeeds only with the use of the azidinium salt 2.
The thermodynamically quite stable diazo compounds 3 a, b are very resistant to mineral acids but can be readily coupled to form azo derivatives with compounds containing an active C-H bond. Hydrolysis of their labile phosphazines 6 a and b readily gives the hydrazones 7 a, b.

We have made an attempt to transfer the results which we found earlier on α-diazo-γ-butyrolactone to include the heterocyclic five-membered ring systems such as pyrazole and isoxazole[2]. The two esters 1 a and b, whose α-position ought already to be activated in such a way as to allow the diazo group to be introduced directly with diazo group transfer agents[3], were selected as model substances. The diazo transfer was tested for with tosyl azide and the azidinium salt 2 [3,4], but only the latter compound is suitable for the synthesis. While 2 reacts to the desired diazo compounds 3 a and b in good yield at room temperature even under quite mild conditions - in 1N

+Dedicated to Professor Dr. Adolf Butenandt on the occasion of his seventyfifth birthday.

sulfuric acid - no reaction to 3 a and b was achieved with tosyl azide under these conditions. Diazo transfer with this reagent takes place only in alkaline medium, but simultaneous coupling of the diazo compound formed with the starting product ensues.



1a, b 2 3a, b

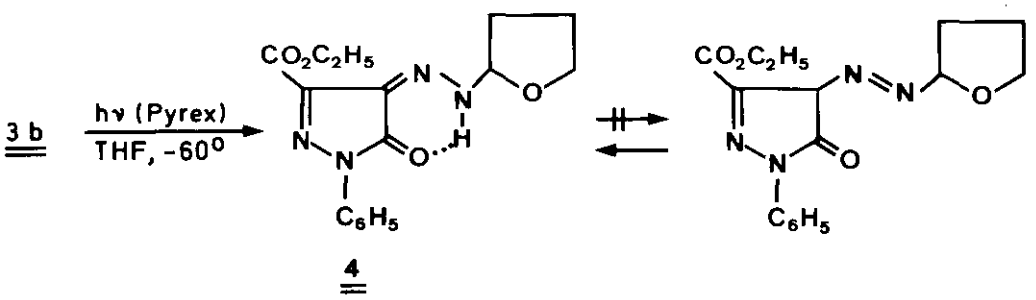
1a (X=O); 1b (X=>N−C$_6$H$_5$)

	X	% yield	mp	IR ($CHCl_3$; cm^{-1}) $-N_2$	C = 0	^{13}C-NMR($CDCl_3$; ppm) 4-C	5-C
3 a	0	60	75°	2150	1760/1720	62.82	170.41
3 b	=N-C_6H_5	76	102°	2140	1740/1680	67.70	162.83

The position of the diazo band in the IR spectrum of 3 a, b indicates quite a high proportion of the diazonium enolate form II in the mesomerism I ↔ II. We were hoping to obtain further information about this mesomerism from the 13-C NMR spectra of the two derivatives. However, the shifts for the carbon atom (4-C) linked to the diazo group are found to be approximately equal to those for diaryldiazomethane[5] or for comparable α-diazo carbonyl compounds[6]. The small signal intensity of the 4-C is attributable to the enhanced negative partial charge on this atom ($\geq C=N_2 \longleftrightarrow \overset{\ominus}{C}-\overset{\oplus}{N}\equiv N|$) and the related long relaxation time.

Both diazo compounds 3 a and b show a relatively high degree of resistance to acids and thermal stress. These properties are more easily explained by a Type II diazonium enolate structure. Thus, on refluxing in xylene 3 a and b

are recovered unchanged. Adding typical diazo cleavage catalysts such as Cu or Ag_2O powder produces no transformation. The high resistance to acids is also noteworthy. In concentrated hydrochloric acid slow decomposition occurs with 3 a only on heating to above 50°, while 3 b is not attacked by concentrated hydrochloric acid even on refluxing. Evidently the mesomeric canonical structure II has such a powerful stabilizing effect that protonation on the diazo carbon atom (4-C) is no longer feasible. Both diazo compounds also resist brief photolysis ($\lambda > 300$ nm) in dioxane, ethanol, benzene, or THF. Irradiation of 10 hours duration is necessary before the diazo product ceases to be detectable. In every case decomposition to a variety of products occurred. The adduct 4 (mp 106°; IR in $CHCl_3$: C=O at 1720/1655, C=N at 1530 cm^{-1}; UV in CH_3OH: 243 nm, log ε = 4.05 and 320 nm, log ε = 4.16) was the only product which could be isolated under varying conditions; it was formed by addition of 3 b to the solvent THF.



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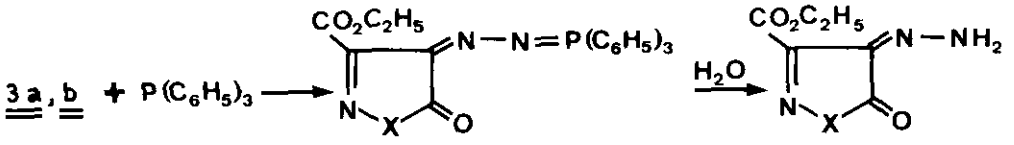
The spectroscopic data exclude the azo form that is tautomeric with the hydrazone structure 4. From the relatively low IR absorption at 1655 cm^{-1} for the pyrazolone carbonyl it seems that chelation in the manner indicated is likely.

When bases such as caustic soda act on 3 b selective saponification of the ester group to the free carboxylic acid 5 (mp 209°; 44% yield; IR (KBr): N_2 at 2170, C=O at 1700/1630 cm^{-1}) takes place without a simultaneous attack on the diazo group. The thermally stable, sublimable carboxylic acid 5 is among the few examples of diazo compounds which at the same time possess a free

carboxylic acid function. The isoxazolone derivative 3 a is decomposed in an undefined manner under alkaline conditions. Here the isoxazolone skeleton represents the more labile part because even the unsubstituted parent compound 1 a is decomposed to polymeric resins under these conditions. Being diazo compounds, 3 a and 3 b undergo the typical phosphazine formation reaction with triphenylphosphine.



6 a, b 7 a, b

	X	mp	% yield	IR ($CHCl_3$) cm^{-1} C=O
6 a	0	159°	90	1730
6 b	=N-C_6H_5	156°	80	1720/1670

The phosphazines 6 a, b formed are red in colour and extremely sensitive to hydrolysis. Water rapidly converts them to the corresponding hydrazones 7 a, b.

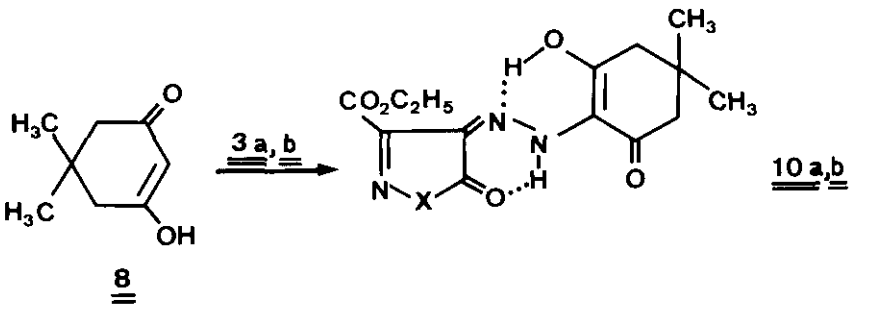
	X	mp	% yield	IR (KBr) cm^{-1} N-H	C=O	C=N
7 a	0	174°	65	3340/3210	1735	1610
7 b	=N-C_6H_5	177°	73	3315/3140	1700	1580

This marked lack of stability of the phosphazines 6 a, b can be attributed to the weakened P=N double bond character produced by the mesomeric equilibrium between the above phosphazines 6 a, b and the corresponding azophosphonium enolates. This phenomenon is clearly evident in the IR spectrum ($CHCl_3$) of 6 b which continues to show a weak diazo band as a consequence

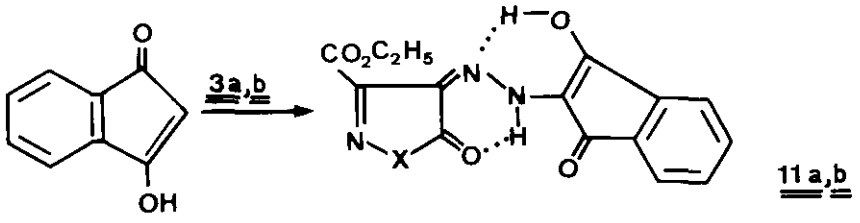
of the dissociation equilibrium 3 a,b ⇄ 6 a,b. Such equilibria have already been observed and investigated in other systems[7]

The hydrazones 7 a,b are very stable. An intramolecular cyclization between the ester carbonyl and the hydrazone groups could not be achieved even under varying reaction conditions (acid, basic, thermal). Furthermore, no reaction to the corresponding hydrazones took place with benzaldehydes, a reaction which we successfully accomplished with α-hydrazono-γ-butyrolactone at an earlier date[2].

With compounds of acid C-H bond character such as dimedone 8 or indandione 9, the diazo compounds 3 a,b readily undergo azo coupling to 10 a,b and 11 a,b in weakly alkaline medium (NaOAc). Whether the orange-red products should be formulated as true azo compounds cannot be decided clearly from the spectroscopic data.



8 10 a,b



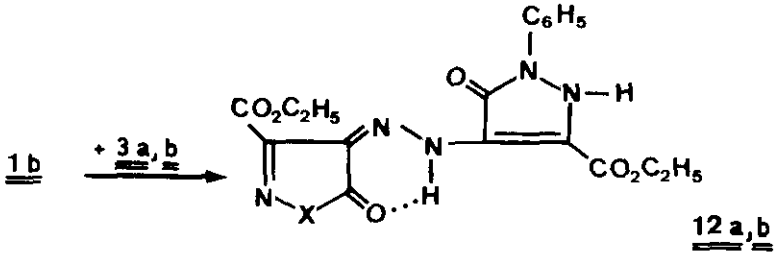
9 11 a,b

	X	mp	% yield	IR (KBr) cm^{-1} N-H	C=O	λ (CH_3OH) in nm; log ε in parentheses
10 a	0	140°	93	3150	1720/1650	290 (3.71); 445 (4.19)
10 b	=N-C_6H_5	198°	76	3100	1720/1695/ 1650	258 (4.19); 490 (4.23)
11 a	0	174°	73	3300	1740/1700/ 1650	240 (4.29); 505 (4.34)
11 b	=N-C_6H_5	214°	47	3250	1720/1690/ 1660	245 (4.41); 460 (4.26)

The N-H band is weak and wide

Overall each of these compounds can occur in at least 13 tautomeric forms. On the evidence of the IR spectra and the ready formation of an intramolecular hydrogen bond we favour the formula reproduced above. Because of the long-wave absorption maxima which occur the UV spectra do not, however, rule out an azo structure. We have not yet investigated in detail how far equilibria between the different tautomeric forms are present, more especially as the solvent used should exercize a strong effect here as well.

Under the coupling conditions the diazo compounds 3 a, b also react with the pyrazolone ester 1 b to form the compounds 12 a and 12 b. The structure of these compounds can be postulated to be as is shown in the following scheme for reasons of analogy[8]. A precise assignment to one of the many tautomers is again difficult, though, because other factors such as solvents, temperature, or pH have a considerable effect on the equilibria.



12 a,b

	X	mp	% yield	IR (KBr) cm^{-1} C=0	λ (CH_3OH) in nm; log ε in parentheses
12 a	0	181°	77	1720/1700	255 (4.20); 515 (4.34)
12 b	=N-C_6H_5	277°	60	1725/1695/1655	255 (4.13); 520 (4.02)

The isoxazolone ester 1 a cannot be made to react in the same way because it decomposes already in the weakly alkaline reaction medium.

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