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SOLVENT-DERIVED PRODUCTS FROM REACTIONS OF PHENYL ISOCYANATE IN DIMETHYL SULFOXIDE

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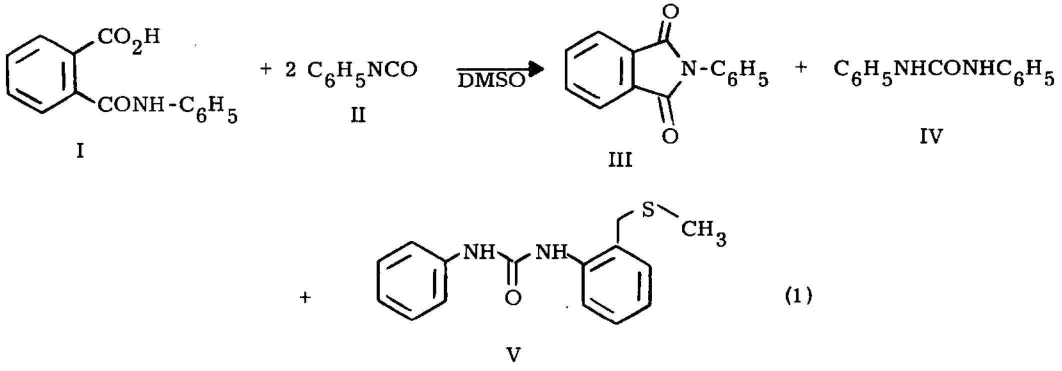
In pyridine or benzene dehydration of phthalanilic acid (I) in the presence of two equivalents of phenyl isocyanate (II) gives equivalent amounts of N-phenylphthalimide (III) and 1, 3-diphenylurea (IV). However, in DMSO at 25°, N-(o-thiomethoxymethyl)-N'-phenylurea (V) is found in 30% yield (eqn. 1) along with III (44%), IV (63%) and recovered I (36%). Traces of phthalic anhydride are also present.



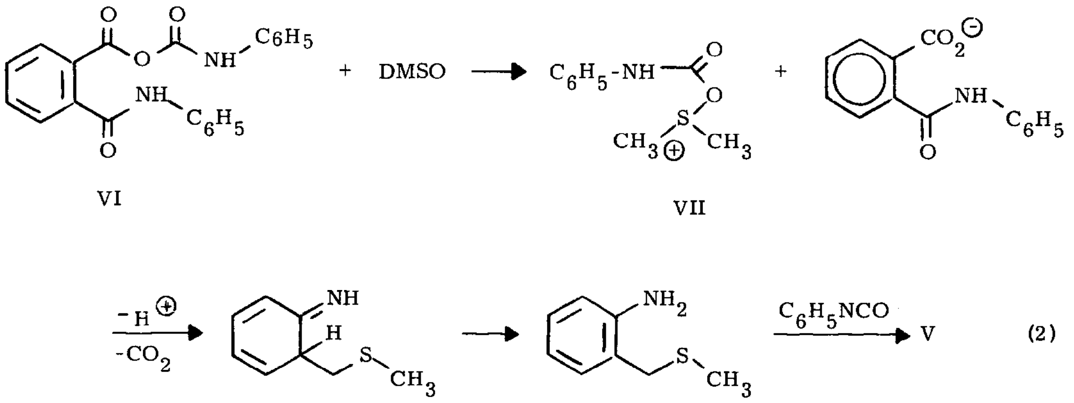
(1)

The structure of V (m.p. 155-155.5°) is indicated by mass spectral analysis (m/e 272, 70 eV)(1), a satisfactory elemental analysis, nmr (DMSO-d_6, 60 MHz: δ 9.13 (singlet, 2H), 7.91 (broad singlet, 2H), 6.9-7.6 (multiplet, 7H), 3.75 (singlet, 2H) and 1.97 ppm (singlet, 3H), and infrared ($CHCl_3$: 2.92μ, NH; 5.95μ, broad, C=O; 6.57μ, CO-NH; 6.91μ, 7.61μ-CH_3). Desulfurization with Raney nickel (2) yields N-phenyl-N'-o-tolylurea, m.p. 198-199.5°, m.m.p. (with authentic tolylphenylurea) 198-202°.

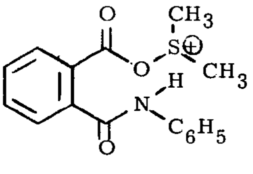
Oxidations with dimethyl sulfoxide (3, 4) involve an intermediate dimethylsulfoxonium salt (5) formed by addition of DMSO to a generalized anhydride. Thus dicyclohexylcarbodiimide (6), alkyl chloroformates (7), acetic anhydride (8), phosphorus pentoxide (9), sulfur trioxide (10), and most recently, mercuric acetate (11) have been used successfully with DMSO as mild oxidants.

The reaction of a carboxylic acid with an isocyanate has been shown to form a mixed carboxylic-carbamic anhydride (12, 13, 14). Accordingly, the anhydride formed in situ from benzoic acid and phenyl isocyanate (9b, 16), reacts with DMSO to give after rearrangement 60% thiomethoxymethylbenzoate. This ester arises from attack of DMSO at the "acid" carbonyl of the mixed anhydride.

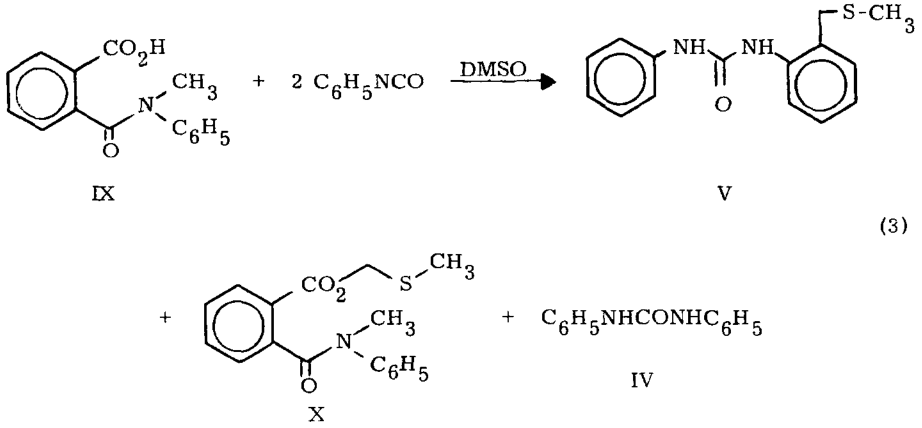
The formation of V is most easily explained by reaction of DMSO at the "urethane" carbonyl of VI, forming a sulfoxonium salt (VII) and phthalanilate (eqn. 2). In the absence of easily oxidizable molecules, the salt VII can either undergo Pummerer rearrangement (17) or cyclize with elimination of carbon dioxide. A third choice would involve elimination of carbon dioxide in a four-centered transition state leading to a sulfimide (18, 19). Neither the Pummerer product nor the sulfimide have been detected.


VI VII (2)

No ester analogous to Sorenson's (16) or Onodera's (9) could be found, perhaps because the sulfoxonium salt (VIII) formed by attack at the "acid" carbonyl readily loses a proton and a molecule of solvent to form N-phenylphthalimide. However, N-methylphthalanilic acid (IX) in which imide formation is prevented reacts with phenyl isocyanate in DMSO to give both the alkylated urea V and the rearrangement product X. At 25° the products are V (50%), IV (26%),


VIII

starting acid (26%) and thiomethoxymethyl o-(N-methylphthalanilate)(X, 30%). The oily ester was not isolated, but was determined admixed with V by nmr. The isolation of V in this case was accomplished by alkaline hydrolysis of the mixture and separation of the urea and N-methylphthalanilic acid.



(3)

The characterization of the ester X depends upon its nmr and ir spectra and its hydrolysis. Resonances (CCl_4, 60 MHz) at 1.72δ (singlet), at 5.14δ (singlet) in the ratio 3:2 are assigned to the thiomethoxymethyleneoxy group (6b, 6c), while the N-methyl is a broad singlet at ~3.4δ and the aromatic protons appear between 6.7 and 7.7δ. Infrared absorptions at 5.82μ and 6.10μ (C=O), at 8.0 and 9.0μ (phthalate) and at 7.6μ ($S-CH_3$) identify the molecule further.

That the mixed anhydride is involved in these reactions and not the starting materials separately is attested to by the following control reactions. Diphenylurea is recovered unchanged in 98% yield after heating with DMSO at 120° for 112 hrs. Phenyl isocyanate in DMSO at 120° for 136 hrs gives 16% urea, 37% triphenyl isocyanurate and 16% starting material. After 24 hrs at 120°, phthalanilic acid is simply dehydrated to imide (93%), leaving 3% (recovered) starting acid. N-Methylphthanilic acid and diphenylurea in DMSO under the reaction conditions are inert.

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References

1. We would like to thank R. Wnuk, The Upjohn Company, Kalamazoo, Michigan, for mass spectral data.
2. R. Mozingo, D.E.Wolf, S.A.Harris and K.Folkers, J. Amer. Chem. Soc. 65, 1013 (1943).

3. (a) N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand and W. M. Weaver, *ibid.* **79**, 6562 (1957).
   (b) N. Kornblum, W. J. Jones and G. J. Anderson, *ibid.* **81**, 4113 (1959).
4. W. W. Epstein and F. W. Sweat, *Chem. Rev.* **67**, 247 (1967).
5. (a) S. G. Smith and S. Winstein, *Tetrahedron* **3**, 317 (1958).
   (b) I. M. Hunsberger and J. M. Tien, *Chem. Ind.* (London), 88 (1959).
   (c) N. R. Nace and J. J. Monagle, *J. Org. Chem.* **24**, 1792 (1959).
   (d) K. Torssell, *Tetrahedron Lett.* 4445 (1966); *Acta Chem. Scand.* **21**, 1 (1967).
6. (a) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.* **85**, 3027 (1963); *ibid.* **87**, 5661 (1965); *ibid.* **87**, 5670 (1965).
   (b) M. G. Burdon and J. G. Moffatt, *ibid.* **87**, 4656 (1965); **88**, 5855 (1966); *ibid.* **89**, 4725 (1967).
   (c) K. E. Pfitzner, J. P. Marino and R. A. Olafson, *ibid.* **87**, 4658 (1965).
7. D. H. R. Barton, B. J. Gardner and R. H. Wrightman, *J. Chem. Soc.*, 1855 (1964).
8. (a) J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.* **87**, 4214 (1965); *ibid.* **89**, 2416 (1967).
   (b) G. R. Pettit and T. H. Brown, *Can. J. Chem.* **45**, 1306 (1967).
   (c) Y. Hayashi and R. Oda, *J. Org. Chem.* **32**, 457 (1967).
9. (a) K. Onodera, S. Hirano and N. Kashimura, *J. Amer. Chem. Soc.* **87**, 4651 (1965).
   (b) K. Onodera, S. Hirano, N. Kashimura and T. Yajima, *Tetrahedron Lett.* (48), 4327 (1965).
10. J. R. Parikh and W. von E. Doering, *J. Amer. Chem. Soc.* **89** (21), 5505 (1967).
11. J. M. Tien, H. J. Tien and J. S. Ting, *Tetrahedron Lett.* (19), 1483 (1969).
12. C. Naegeli and A. Tyabji, *Helv. Chim. Acta* **18**, 142 (1935).
13. J. A. Parker, J. J. Thomas, C. L. Fieze, E. A. Peterson and R. P. Dryden, Report to 132nd Meeting of the American Chemical Society, New York, Sept. 8-13, 1957; p. 63P.
14. C. Naegeli and A. Tyabj, *Helv. Chim. Acta* **17**, 931 (1934).
15. W. D'Olieslager and I. DeAguirre, *Bull. Soc. Chim. France* **1967**, 179.
16. W. R. Sorenson, *J. Org. Chem.* **24**, 978 (1959).
17. R. Pummerer, *Chem. Ber.* **43**, 1401 (1910).
18. P. Claus and W. Vycudlik, *Tetrahedron Lett.* (32), 3607 (1968).
19. C. King, *J. Org. Chem.* **25**, 352 (1960).