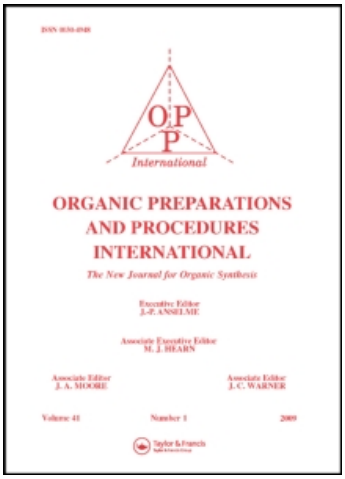


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

THE SYNTHESIS OF 2,4[1H,3H]QUINAZOLINEDIONE AND SOME OF ITS 3-ARYL SUBSTITUTED DERIVATIVES

M. Michman[a]; S. Patai[a]; Y. Wiesel[a]
[a] Department of Organic Chemistry, The Hebrew Univesrity, Jerusalem, ISRAEL

To cite this Article Michman, M. , Patai, S. and Wiesel, Y.(1978) 'THE SYNTHESIS OF 2,4[1H,3H]QUINAZOLINEDIONE AND SOME OF ITS 3-ARYL SUBSTITUTED DERIVATIVES', Organic Preparations and Procedures International, 10: 1, 13 — 16
To link to this Article: DOI: 10.1080/00304947809354998
URL: http://dx.doi.org/10.1080/00304947809354998

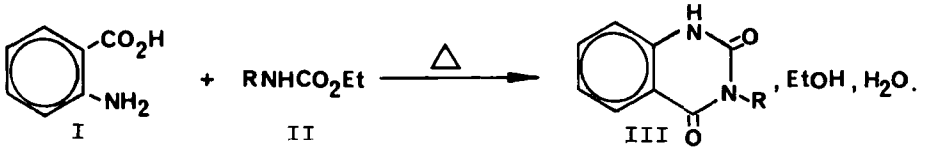
ORGANIC PREPARATIONS AND PROCEDURES INT. 10(1), 13-16 (1978)

THE SYNTHESIS OF 2,4[1H,3H]QUINAZOLINEDIONE AND SOME OF ITS 3-ARYL SUBSTITUTED DERIVATIVES

M. Michman*, S. Patai and Y. Wiesel
Department of Organic Chemistry
The Hebrew Univesrity, Jerusalem, ISRAEL

3-Aryl-2,4[1H,3H]quinazolinediones (III) have been described as herbicides[1], while others were reported to affect the nervous system.[2] Some of these compounds have been used in the therapeutic treatment of allergic and inflammatory symptoms in man.[3,4]

The fusion of anthranilic acid and urethane at 180° for 16 hrs in the molar ratio of 1:3 gave 2,4[1H,3H]quinazolinedione in 60% yield. The yield dropped to 33% when the reaction was carried out at 160°. Unidentified side products, some ammonia and carbon dioxide were formed, probably due to self-condensation of urethane. However, the addition of imidazole, which was shown to have catalytic effects in similar reactions im melts,[5] reduced the side reactions. A series of 3-aryl derivatives of 2,4[1H,3H]-quinazolinedione have been prepared by fusing the corresponding N-aryl-carbamates with anthranilic acid. The similarity of transacylation at the amide nitrogen of the carbamate to the transacylations of amides has been demonstrated in a previous paper.[6] In the present case, the amido



I II III

R = H; C_6H_5-; 4-$CH_3C_6H_4$-; 4-ClC_6H_4-; 3ClC_6H_4; 4-$CH_3OC_6H_4$-; 4-$O_2NC_6H_4$-;

nitrogen of the carbamate is acylated and the thermal condensation to quinazolinedione follows in a pattern which is known for other pyrimidine syntheses.[7] Thus transacylation in the melt offers a simple, straightforward preparation of quinazolinediones. To the best of our knowledge such preparation of quinazolinediones from carbamates and anthranilic acid has not been reported previously.

Methods for the preparation of quinazolinediones include modifications of the Niementowski reaction[8] such as the fusing of anthranilic acid with urea[9] or its reactions with isocyanates,[10] the Hoffman reaction of hypobromous acid on phthalhydrazide,[11] or the cyclisation of ethoxycarbonylaminobenzonitrile with sodium methoxide.[12]. These and other methods, such as the direct oxidation of quinazoline have been reviewed.[13] 3-Aryl derivatives have been prepared by the condensation of N-arylureas with anthranilic acid[6,14] or by the condensation of aniline derivatives with CO_2 at 200° under a pressure of 6.000-8.500 atm.,[15] or from azobenzene with CO.[16] Some of these methods give irreproducible yields,[10] tend to yield side products[9] or are complicated.[15,16] The present method is simple and straightforward, by-products and starting material being easily removable.

The mass spectra of these compounds show an abundance of even-electron ions as a result of typical rearrangements, i.e., fragments of even mass for the first four aryl derivatives and odd masses for the nitrophenyl derivative (Table I). In all compounds, the high abundance of m/e 118 and 146 may be attributed to the fragments $[C_6H_4(CO)NCO]^+$ and $[C_6H_4NCO]^+$ from rearrangement of the benzpyrimidine structure. This common pattern is independent of the substituent at N^3 and has therefore a diagnostic value for this series of compounds. By comparison, the unsubstituted quinazolinedione gives a different fragmentation pattern which makes this test more decisive. A clear indication that the N^3 atom is substitu-

ted is the fact that no fragments suggesting diarylamine structures are observed.

Table I: Mass spectra of 3-aryl-2,4[1H]quinazolinediones[a]

R	M+ (%)					
H	162 (92)	119(100)	92(69)	149 (9)		
4-$CH_3C_6H_4$-	252(100)	118 (97)	146(84)	92(32)	64(17)	238(13)
4-ClC_6H_4-	272 (79)	118(100)	146(92)	92(26)	64(12)	-
3-ClC_6H_4	272 (75)	118(100)	146(88)	92(38)	64(15)	-
4-$CH_3OC_6H_4$	268 (58)	118(100)	107(96)	76(81)	146(69)	92(69)
	64 (31)	197(24)				
4-$O_2NC_6H_4$-	283 (62)	118(100)	146(80)	125(62)	253(52)	92(37)
	276 (26)					

[a] Molecular peak underlined, fragments (> 5%) in the order of decreasing intensity.

EXPERIMENTAL

N-Arylcarbamates.-N-Arylcarbamates were prepared by the reaction of ethyl chloroformate with the corresponding aromatic amine in pyridine.[17] All gave satisfactory analysis and mps. coinciding with literature data.

2,4-[1H,3H]Quinazolinedione.-A finely ground mixture of anthranilic acid (10.96g, 0.08 mole) and ethyl carbamate (21.3g, 0.25 mole) was heated under reflux with stirring at 180° for 16 hrs,while ammonia and carbon dioxide were evolved. The collected liquid distillate was ethanol and water. The residue was cooled and unreacted ethyl carbamate removed from the mixture by treatment with ether. The residual solid was washed with sat. $NaHCO_3$ solution, then with alcohol (by crunching in a mortar). Filtration and recrystallization from water left 6.4g, (60%) of 2,4-[1H,3H]quinazolinedione mp. > 349° lit.[9] mp. > 350°. Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28 Found: C, 59.47; H, 3.73; N, 17.40%. When the reaction was conducted at 160°, the yield decreased to 33%. Imidazole catalysed reactions were carried out by heating to 150° for 24 hrs, a mixture of an-

thranilic acid (0.02 mole), carbamate (0.02 mole) and imidazole (0.02 mole).

The 3-Aryl-2,4-[1H]quinazolinediones were simply prepared by heating the proper mixture at 150° for 24 hrs. The results are summarized below. C_6H_5- mp. 275 lit.[16] 275; 4-$CH_3C_6H_4$-, mp. 261-263°, lit. 263-265, (50% yield); 4-ClC_6H_4- mp. 301° lit. 299-301[1]; 279[3] (50%); 3-ClC_6H_4- mp. 271° lit. 269-270[1], 256[2] (83%); 4-$CH_3OC_6H_4$- mp. 297° lit. 293[1] (50%); 4-$O_2NC_6H_4$- mp. > 300° lit. 375[3] (40%). All gave satisfactory analyses.

ACKNOWLEDGMENT.-This research was sponsored in part by the European Research Office, United States Army, London, England.

REFERENCES

1. P. Winternitz, P. Papos and J. Synak. Czech. Patent 128.433, 1968, CA 70, 115176z (1969).
2. S. Toyoshima, K. Shimada, S. Hamano and T. Ogo, Yakugaku Zasschi, 85, 502, (1965).
3. D. M. Omant, Brit. Patent 1059271, 1967, CA, 67, 54161e, (1967).
4. W. Hepworth in "Reports on the Progress of Applied Chemistry", 59, p. 524, Blackwell Scientific Pub., 1974.
5. L. Kardosh, M. Krasnoselsky and S. Patai, Israel J. Chem., 7, 111, (1969).
6. Y. Wiesel, S. Patai and M. Michman, J. Chem. Soc. Perkin I, 1705, (1977).
7. M. H. Palmer, "The Structure and Reactions of Heterocyclic Compounds", p. 79, Edward Arnold, London, 1967.
8. G. M. Badger in "The Chemistry of Heterocyclic Compounds, p. 389. Academic Press, 1961; S. Niementowski, Ber., R516, (1894).
9. F. E. Sheibley, J. Org. Chem., 12, 743, (1947).
10. N. A. Lange and F.E. Sheibley, Org. Syn. Coll. Vol. II, 79, 1943.
11. A. Albert, "Heterocyclic Chemistry", p. 178, The Athlone Press, London, 2nd Ed., 1968.
12. K. W. Breukink and P.E. Verkade, Rec. Trav. Chim., 79, 443 (1960).
13. W. L. F. Armarego, "Adv. Heterocyclic Chem.", (A. R. Katritzky, Ed.), Vol. I, pp. 262 and 294, Academic Press, 1963.
14. C. Paul, Ber., 27, 1877, (1894); Br. Pawlewski, ibid., 38, 131 (1905); F. Kunckell, ibid., 43, 1237 (1910).
15. T. L. Cairns, D. D. Coffman and W. W. Gilbert, J. Am. Chem. Soc. 79, 4405, (1957).
16. S. Murahashi and S. Horiie, ibid., 78, 4816 (1956).
17. P. Adams and F. A. Baron, Chem. Rev., 65, 569 (1965).

(Received August 16, 1977; in revised form November 14, 1977)