Tetrahedron Letters No. 4, pp 331 - 334.
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0040-4039/79/0122-0331$02.00/0

ANTHRACYCLINES AND RELATED SUBSTANCES I. A NEW FRIEDEL-CRAFTS ALKYLATION REACTION USING 3-BROMOPHTHALIDES. EFFICIENT SYNTHESIS OF ISLANDICIN.

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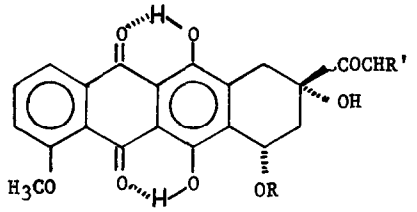
Approaches to the total synthesis of the aglycones 1 and 2 respectively of the anti-tumor compounds daunomycin 3 and adriamycin 4, have been plagued by problems of regio-specificity and/or low overall yields.



1 R,R'=H
2 R=H;R'=OH
3 R =H;R'=l-daunosaminyl
4 R =OH;R'=l-daunosaminyl

Our research in this area has been devoted to solving the first of these problems and in this paper we present the results of our preliminary investigations.

The synthesis of anthraquinones 4 and its higher homologs is generally accomplished[1] by the two-step double acylation of aromatic substrates with phthalic anhydrides under Friedel-Crafts conditions (Scheme I). However the method has two drawbacks. It lacks regiospecificity when the anhydride 1 is unsymmetrically substituted, and the second acylation (3→4) is very difficult to accomplish unless the aromatic substrate is highly activated. The latter problem can be circumvented[2,3] by reduction of 3 first to 5 then to 6, followed by facile cyclization to 7 and then oxidation of the latter to 4. The problem of regiospecificity can be solved by the condensation[4] of the appropriate phthaldehydic acid 8 with 2 to give 5. However this approach constitutes only a limited solution because the yields of 5 are variable[5], purification of the product is often tedious[5] and many groups could not survive the concentrated sulfuric acid required to bring about reaction.

We have now found that a variety of 3-arylphthalides 11 can be prepared in good to excellent yield by the reaction of 3-bromophthalides[6,7] 9 with an aromatic substrate 10 in the presence of stannic chloride in methylene chloride solution at ice-bath temperatures.

Scheme I

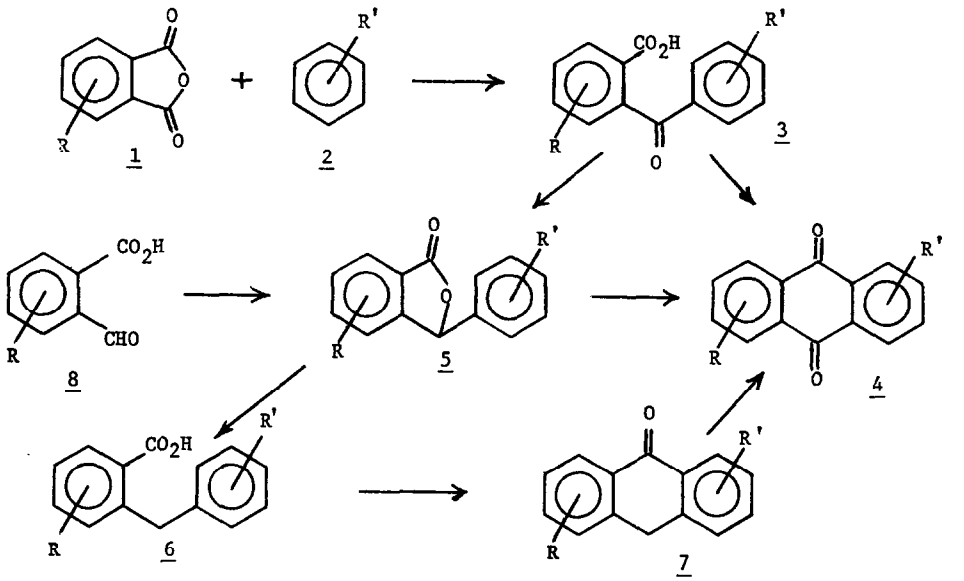
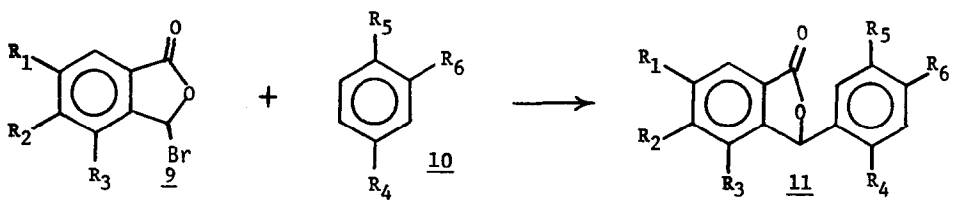


Table:Preparation of 3-Arylphthalides

No	R_1	R_2	R_3	R_4	R_5	R_6	Yield (%)	mp(^{o}C).
11a	H	H	H	OCH_3	OCH_3	H	60	80
11b	H	H	H	OCH_3	OCH_3	Cl	70	151-152
11c	H	H	H	OCH_3	OCH_3	Br	70	168-169
11d	H	H	OCH_3	OCH_3	OCH_3	H	83	133-135
11e	H	H	OCH_3	OAc	OAc	H	60	153-154
11f	H	H	OCH_3	OCH_3	OCH_3	Cl	85	180-181
11g	H	H	OCH_3	OCH_3	OCH_3	Br	85	195-197
11h	H	H	OCH_3	OCH_3	OCH_3	CH_3	75	161-164
11i	OCH_3	OCH_3	OCH_3	H	Br	OCH_3	75	135-136
11j	OCH_3	OCH_3	OCH_3	H	CH_3	OCH_3	94	129.5-130.5

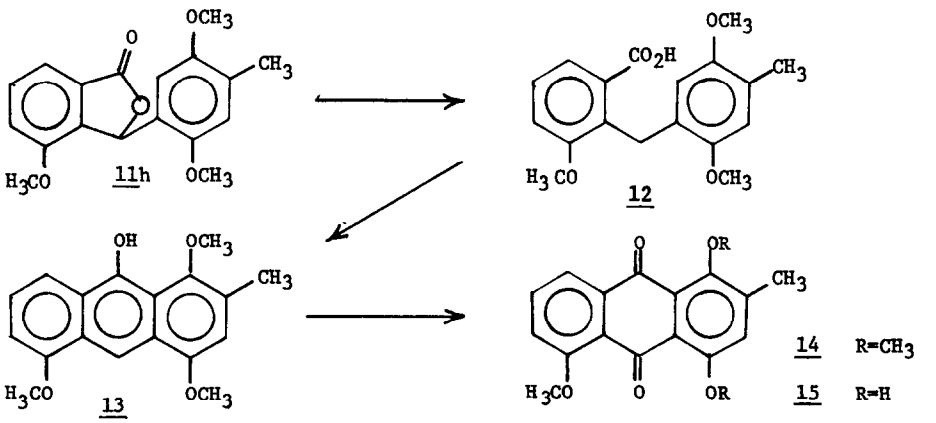


Some of our results are shown in the Table above.

An interesting aspect of this alkylation is that the 3-phthalido group, regarded as a substituent on an aromatic ring, appears to exert an inductively deactivating effect. Support for this postulate lies in the fact that in most cases that we have examined no products of double alkylation are obtained if equimolar quantities of 9 and 10 are used. (This is in contrast to preparation of 3-arylphthalides via the use of phthalaldehydes and H_2SO_4 as the catalyst). Only in the case of 3-bromophthalide and 1,4-dimethoxybenzene did small amounts (<10%) of a bis-alkylated substance accompany the main product 11a. This substance could also be obtained in good yield (70%) by using two equivalents of 3-bromophthalide in the reaction or by the reaction of one equivalent of the latter with 11a, provided that extended reaction times were used.

At least one source of the deactivating inductive effect appears to be the oxycarbonyl group of the phthalide moiety. This may be likened to the deactivating effect that chlorine has (in nitration reactions) when substituted in the α-position of an aralkane[8]. It is also possible that the stannic chloride catalyst, by coordination with the phthalide carbonyl of the initial product (11) partially ionizes the adjacent benzylic oxygen, thus reducing the reactivity of the aromatic ring. Further experimentation is needed however to resolve the origin of this deactivation.

All of the compounds listed in the Table can be converted[9] to the corresponding anthracenes or anthraquinones. However, we report here only one example, namely the conversion of 11h to islandicin 15 by new procedures which are highly efficient. Reduction of 11h with triethylsilane in trifluoroacetic acid (12 hours at room temperature) afforded the benzylbenzoic acid 12 in 95% yield and this compound when treated with trifluoroacetic anhydride in trifluoroacetic acid for 20 min at 25° afforded 13 (as mixture of anthrone and



anthranol tautomers-mainly the latter) in almost quantitative yield. Oxidation of 13 with chromium trioxide in acetic acid at reflux[3] then yielded islandicin trimethyl ether 14 in 50% overall yield from 12. Demethylation[10] of 14 to give islandicin[11] 15 was accomplished in 79% yield by means of aluminum chloride in nitrobenzene (2 days at 90°). The physical and spectroscopic characteristics of 15 and its triacetate were identical to those reported in the literature[12].

The application of these methods to an efficient preparation of 7,9-dideoxydaunomycinone, a key intermediate in the synthesis of I, will be the subject of a future publication[13].

Acknowledgement. The authors would like to express their thanks to the National Cancer Institute for a grant (No. CA20197) in aid of this work, and to Dr. F. Arcamone of Farmitalia for a generous financial donation. The able technical assistance of Miss N. Stambler and Mr. John Winter is gratefully acknowledged.

References & Notes

1. S. Sethna in Friedel-Crafts and Related Reactions Vol. 3 (Ed. G.A. Olah) Interscience, New York, (1964) p 940; J. Houben and W. Fischer, Das Anthracen and Die Anthrachinone, Georg Thieme Verlag, Leipzig, (1927).
2. A. Bistrzycki and K. Krauer, Helv. Chim. Acta., 6, 750 (1923).
3. M. G. Sarngadharan and T. R. Seshadri, Indian J. Chem., 4, 503 (1966).
4. A. Bistrzycki and D. W. Yssel de Schepper, Ber. Dtsch. Chem. Ges., 31, 2790 (1898).
5. M. M. Brubaker and R. Adams, J. Amer. Chem. Soc., 49, 2279 (1927).
6. Y. Hirshberg, D. Lavie and E. D. Bergman, J. Chem. Soc., 1030 (1951); J.J. Brown and G.T. Newbold ibid., 4397 (1952).
7. V.E. Maekawa and S. Nan'ya, Bull. Chem. Soc. Japan, 32, 1311 (1959).
8. C.K. Ingold and F.R. Shaw, J. Chem. Soc., 575 (1949); J.R. Knowles and R.O.C. Newman ibid., 2938 (1961); F.L. Riley and E. Rothstein ibid., 3860 (1964).
9. Details of this work will appear in the full publication.
10. Trimethylsilyl iodide also successfully demethylated 14 to give 15 in 80% yield. However the use of BBr_3 for this purpose led to a mixture of partially and fully demethylated products (cf ref. 11a).
11. Two other syntheses of islandicin have been published (a) A.S. Kende, J.L. Belletire and E.L. Hume, Tetrahedron Lett., 31 2935 (1973); (b) R.D. Gleim, S. Trenbeath, F. Suzuki and C.J. Sih, J. Chem. Soc. Chem. Comm., 242 (1978). However their overall yields of 15 are very low compared with the 25% reported here.
12. B.H. Howard and H. Raistrick, Biochem.J., 44, 227 (1949).
13. This work and some of the results reported in this paper were presented at the "Symposium on Chemistry of Antitumor Anthracyclines". The 61st Chemical Institute of Canada Conference Winnipeg, June 4-7, 1978.

(Received in USA 3 October 1978)