THE FORMATION OF AZULENO[2,1-d]PYRIMIDINE DERIVATIVES BY THE REACTION OF 2-ACETYLIMINO-2H-CYCLOHEPTA[b]FURAN DERIVATIVES WITH ACTIVE METHYLENE COMPOUNDS[1]

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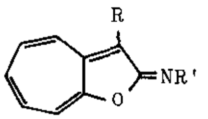
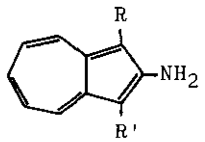
Abstract: The reaction of 2-acetylimino-2H-cyclohepta[b]furan derivatives with some active methylene compounds directly gave azuleno[2,1-d]pyrimidine derivatives, which were also synthesized from 2-amino-1-carbamoylazulenes.

There has been found a novel and efficient method of azulene synthesis from troponoid[3] or 2H-cyclohepta[b]furan-2-one derivatives,[4] utilizing the reaction with active methylene compounds, such as malononitrile (MNL), cyanoacetamide (CAA), ethyl cyanoacetate (ECA), and diethyl malonate (DEM). The mechanisms of such unusual synthetic reactions have also been discussed.[4] Moreover, it has been found that azulene derivatives fused with heterocycles, namely azuleno[2,1-b]pyrid-2(1H)-one derivatives were directly obtained on application of such synthetic reactions to 3-(2-ethoxycarbonyl-1-oxoethyl)-2H-cyclohepta[b]furan-2-one.[5] In order to obtain an additional information on the reaction mechanisms of such unusual azulene formation, the present authors have studied on the reaction of 2-acetylimino-3-cyano- (**1a**)[6,7] and 2-acetylimino-3-carbamoyl-2H-cyclohepta[b]furans (**1b**)[6] with active methylene compounds and found that azuleno[2,1-d]pyrimidin-4(3H)-one derivatives were directly obtained from **1a**,**b**.

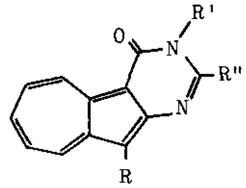
The treatment of **1a** with MNL in the presence of sodium ethoxide in ethanol at room temperature gave 2-amino-1,3-dicyanoazulene (**2a**) in 10% yield, together with 3-cyanocyclohepta[b]pyrrol-2(1H)-one (**3a**) [yellow needles, mp 313°C (decomp.); lit.,[8] mp 305°C (decomp.)] in 32% yield. When t-butylamine was used as the base, only **2a** was obtained in 88% yield. A similar treatment of **1a** with CAA gave no azulenic compound, except for an unidentified substance. On the other hand, the treatment of 1a with ECA in the presence of sodium ethoxide yielded 10-cyano-2-methylazuleno[2,1-d]pyrimidin-4(3H)-one (4a) [reddish orange crystals, mp over 300°C; ir (KBr): 2208 (C≡N), 1653 cm⁻¹ (C=O)] in 19% yield, together with 3a in 51% yield. In the case of 1b, the reaction with MNL and CAA gave 4a and 10-carbamoyl-2-methylazuleno[2,1-d]pyrimidin-4(3H)-one (4b) [reddish orange plates, mp over 300°C; ir (KBr): 3380 (NH), 1670, 1630 cm⁻¹ (C=O)] in 72% and 63% yields, respectively. However, the reaction of 1b with ECA gave ethyl 2-amino-3-carbamoylazulene-1-carboxylate (2c) in 4% yield, together with 3-carbamoylcyclohepta[b]pyrrol-2(1H)-one (3b) [yellow crystals, mp 310°C (decomp.); lit.,[8] mp 300°C (decomp.)] in 84% yield.



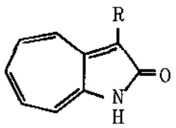
1a: R=CN, R'=$COCH_3$
1b: R=$CONH_2$, R'=$COCH_3$
7a: R=CN, R'=H
7b: R=$CONH_2$, R'=H



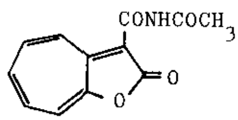
2a: R=R'=CN
2b: R=$CONH_2$, R'=CN
2c: R=$CONH_2$, R'=$CO_2C_2H_5$
2d: R=$CONH_2$, R'=$COCH_3$



4a: R=CN, R'=H, R"=CH_3
4b: R=$CONH_2$, R'=H, R"=CH_3
4c: R=CN, R'=R"=CH_3
4d: R=$COCH_3$, R'=H, R"=CH_3
8a: R=$CO_2C_2H_5$, R'=R"=H
8b: R=$COCH_3$, R'=R"=H



3a: R=CN
3b: R=$CONH_2$



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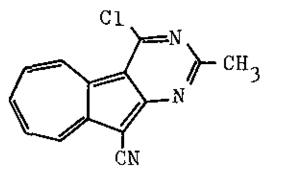

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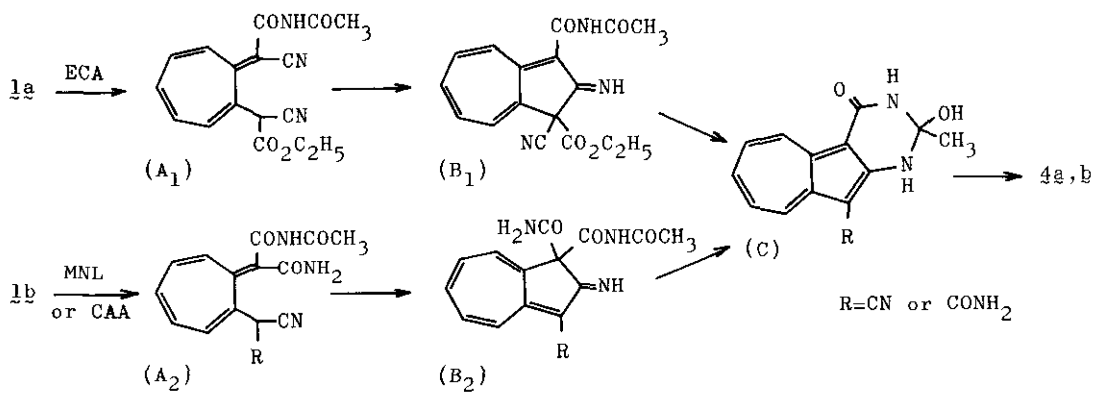
The structures of 4a,b were established on the basis of the chemical evidences described below, as well as the spectral data and elemental analyses.[9] Thus, the treatment of 2a and 2-amino-1-carbamoyl-3-cyanoazulene (2b) with acetic anhydride under reflux gave 4a in 4% and 19% yields, respectively, together with 2-acetamido-1,3-dicyanoazulene [orange crystals, mp 250°C (decomp.); ir (KBr): 3280 (NH), 2212 (C≡N), 1653 cm⁻¹ (C=O)] in 16% and 43% yields, respectively. Further, 4a was also obtained in 88% yield, when 3-acetamidocarbonyl-2H-cyclohepta[b]furan-2-one (5)[10] was treated with MNL in the presence of sodium ethoxide. On the other hand, on methylation with dimethyl sulfate and sodium hydroxide and on treatment with phosphoryl chloride under reflux, 4a gave 10-cyano-2,3-dimethylazuleno[2,1-d]pyrimidin-

4(3H)-one (4c) [orange needles, mp 275°C; ir (KBr): 2212 (C≡N), 1678 cm^{-1} (C=O)] and 4-chloro-10-cyano-2-methylazuleno[2,1-d]pyrimidine (6) [dark violet crystals, mp over 300°C; ir (KBr): 2212 cm^{-1} (C≡N)] in 73% and 56% yields, respectively.

A reaction course for the formation of 4a,b from 1a,b can be presented in Scheme 1, being analogous to that for the formation of azulenes from 2H-cyclohepta-[b]furan-2-ones or -imines.[4] The carbanion produced from MNL, CAA, or ECA attacks on 1a,b at the 8a-position to give heptafulvene-type intermediates (A), which should cyclize to dihydroazulene-type intermediates (B). In the reaction of 1a with ECA, or 1b with MNL or CAA, the elimination of $CO_2C_2H_5$ or $CONH_2$ group in the intermediates (B_1 or B_2) may be accompanied by a simultaneous cyclization between NH and $CONHCOCH_3$ groups, presented in positions favorable to pyrimidine ring formation, to give intermediates (C), which resulted in dehydration to yield 4a,b. The formation of 3a,b may be explained by the lactone ring opening arising from the attack of ethoxide ion, but not carbanions, at the 8a-position in 1a,b, followed by cyclization: this is analogous to the formation of 3a from 2H-cyclohepta[b]furan-2-imine (7a) on alkaline treatment.[7]



Scheme 1. A reaction course for the formation of 4a,b from 1a,b.

Although several papers have appeared on the syntheses of azulene derivatives fused with heterocycles, little is known for the azuleno[2,1-d]pyrimidines.[11] The formation of 4a,b from 1a,b is a facile route for the synthesis of azuleno[2,1-d]-pyrimidine ring system. Moreover, the reaction of 2a with acetic anhydride, leading to the formation of 4a, was also applicable to some 2-amino-1-carbamoylazulenes for the synthesis of azuleno[2,1-d]pyrimidine derivatives. Thus, the treatment of 1-acetyl-2-amino-3-carbamoylazulene (2d)[4] with acetic anhydride and sodium acetate under reflux gave 10-acetyl-2-methylazuleno[2,1-d]pyrimidin-4(3H)-one (4d) [orange crystals, mp over 300°C] in 25% yield. Similarly, the treatment of 2c and 2d with anhydrous formic acid in the presence of acetic anhydride and pyridine at room temperature gave 10-ethoxycarbonyl- (8a) [reddish orange micro-prisms, mp 288°C] and 10-acetylazuleno[2,1-d]pyrimidin-4(3H)-ones (8b) [pale red micro-crystals, mp 345°C (decomp.)] in 86% and 87% yields, respectively.

References and Notes

1. A part of this work was presented at the 18th Annual Meeting of the Chemical Society of Japan, Tokyo, 1965, Abstract p 199; T. Nakazawa, Master Thesis, Tohoku University, 1963.
2. Present address: Tokyo Research Laboratory, Kao Soap Co. Ltd., 2-1-3 Bunka, Sumidaku, Tokyo 131, Japan.
3. a) T. Nozoe, S. Matsumura, Y. Murase, and S. Seto, Chem. & Ind., 1955, 1257; T. Nozoe, S. Seto, S. Matsumura, and Y. Murase, Bull. Chem. Soc. Jpn., 1962, 35, 1179. b) For reviews see, T. Nozoe, Croat. Chem. Acta, 1957, 29, 207; Experientia, Suppl. VII, 1957, 306; T. Nozoe, K. Takase, H. Matsumura, T. Asao, K. Kikuchi, and S. Ito, 'Dai-Yuki-Kagaku (Comprehensive Organic Chemistry)' ed. by M. Kotake, Asakura Publ. Co., Tokyo, 1960, Vol. 13, pp. 178-213, 439-533.
4. a) T. Nozoe, S. Seto, K. Takase, S. Matsumura, and T. Nakazawa, Nippon Kagaku Zasshi, 1965, 86, 346. b) T. Nozoe, Pure Appl. Chem., 1971, 28, 239. c) T. Nozoe, K. Takase, T. Nakazawa, and S. Fukuda, Tetrahedron, 1971, 27, 3357.
5. T. Nozoe, K. Takase, T. Nakazawa, S. Sugita, and M. Saito, Bull. Chem. Soc. Jpn., 1974, 47, 1750.
6. The compounds 1a [yellow needles, mp 148°C; lit.,[7] mp 145°C] and 1b [yellow needles, mp 173°C] were prepared from 3-cyano- (7a)[4a,7] and 3-carbamoyl-2H-cyclohepta[b]furan-2-imines (7b)[4a,7] by acetylation with acetic anhydride, in 76% and 91% yields, respectively.
7. T. Nozoe, T. Mukai, and T. Suzuki, Bull. Chem. Soc. Jpn., 1963, 36, 38.
8. T. Nozoe, S. Seto, and S. Nozoe, Proc. Japan Acad., 1956, 32, 472.
9. Satisfactory elemental analyses and spectral data (uv and ir) were obtained for all new compounds.
10. The compound 5 [yellow micro-needles, mp 220°C (decomp.)] was prepared from 3-carbamoyl-2H-cyclohepta[b]furan-2-one[7] by acetylation with acetic anhydride-conc. sulfuric acid, in 69% yield.
11. See T. Morita, T. Nakadate, and K. Takase, preceeding paper in this issue and references cited therein.

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