Tetrahedron 1966, Vol. 22, pp. 1027 to 1032. Pergamon Press Ltd. Printed in Northern Ireland

STUDIES IN OXASTEROIDS—I

SYNTHESIS OF 3-CYANO-3-METHYL-7-METHOXYCHROMAN-4-ONE AND THE STRUCTURE OF AN "ABNORMAL" PRODUCT

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(*Received* 20 *September* 1965; *in revised form* 16 *October* 1965)

Abstract—A synthesis of 3-cyano-3-methyl-7-methoxychroman-4-one is reported. The structure of an "abnormal" product obtained during isomerization of the isoxazole (III) with potassium t-butoxide in t-butanol followed by alkylation with methyl iodide has been proved to be 3-t-butoxy-2-cyano-2-methyl-2′,4′-dimethoxypropiophenone (IVa).

RECENT interest in the synthesis and study of the physiological activity of oxasteroids[1–7] prompted a stereospecific synthesis of a key-intermediate (I) by the well-known benzhydrindane approach for the construction of *trans*-fused C/D rings.[8,9] The intermediate (I) can be used for further elaboration of 11-oxasteroid analogues. Very recently, Smith *et al.*[4] starting from 7-methoxychroman-4-one achieved a total synthesis of 6-oxaestrone, 6-oxa-8-isoestrone and 6-oxa-8-iso-17-estradiol-3-monomethyl ether, the latter showing 66% of the activity of estradiol.

7-Methoxychroman-4-one[10] was condensed with ethyl formate to give the corresponding 3-formyl derivative in 95% yield. This was converted to the isoxazole (III) in 80% yield.[8] The UV [λ_{max} 234 (ε 13,090), 278 (9925), 286 (10,050) and 318 mμ (12,200)] and the IR [($CHCl_3$) 1658 (C=N), 1613 and 1575 cm^{-1} (aromatic C=C)] spectra of III are in agreement with the expected structure. The NMR spectrum of III which shows signals at 228·5 (3H, —OCH_3), 322 (2H, —OCH_2), 405·5 (2H, multiplet), 450·5 (1H, doublet, J = 9 c/s) and 486·5 c/s (1H, —N=C—H) proved its structure beyond doubt. Initially, the isomerization of III followed by methylation was carried out according to Johnson's conditions and the crude neutral product, isolated from the reaction mixture,[11] was chromatographed on activated Brockman alumina. The fraction eluted with 1:1 petroleum ether–benzene gave a white crystalline solid (45% yield) with UV max at 232, 271 and 299 mμ and IR (nujol) peaks, 2273 (C≡N), 1678 (C=O conjugated) and 1613 and 1575 cm^{-1} (aromatic C=C). Even

[1] G. R. Pettit and T. R. Kasturi, *J. Org. Chem.* **26**, 4557 (1961).
[2] G. R. Pettit, A. K. Das Gupta and U. R. Ghatak, *Steroids* **1**, 137 (1963) and Refs cited therein.
[3] R. Pappo and C. J. Jung, *Tetrahedron Letters* 365 (1962).
[4] H. Smith, G. H. Douglas and C. R. Walk, *Experientia* **20**, 418 (1964).
[5] S. Rakhit and M. Gut, *J. Org. Chem.* **29**, 229 (1964).
[6] G. V. Bhide, N. L. Tikotkar and B. D. Tilak, *Tetrahedron* **10**, 223 (1960).
[7] S. D. Levine, *Tetrahedron Letters* 2233 (1965).
[8] W. S. Johnson, J. W. Peterson and C. D. Gutsche, *J. Amer. Chem. Soc.*, **67**, 2274 (1945); **69**, 2942 (1947).
[9] D. K. Banerjee, S. Chatterjee, C. N. Pillai and M. V. Bhatt, *J. Amer. Chem. Soc.* **78**, 3769 (1956).
[10] E. M. Padfield and M. L. Tomlinson, *J. Chem. Soc.* 2272 (1950).
[11] Investigations on the nature of the other products obtained from this mixture are in progress.

though the aforementioned spectral characteristics correspond to the expected cyanomethylchromanone (IIa), yet the elemental composition of this compound was found to be $C_{17}H_{23}NO_4$ implying the formation of an "abnormal" product during this isomerization. Speckamp *et al.*[12] reported a cleavage product (Va) of the cyanomethyl ketone (IIb) during Stobbe condensation. Similar ring cleavage was earlier observed during Stobbe condensation by Johnson,[8] Tilak *et al.*[13] and Subrahmanyam.[14] In the light of these observations, we presumed at first that a similar cleavage of the initially formed IIa would give rise to Vb. The reaction product, however, on reduction with sodium borohydride gave a hydroxy compound (IVb) with no IR absorption corresponding to ester carbonyl, thus disproving the structure Vb for this abnormal product. The benzylic nature of the carbonyl group was indicated by hydrogenolysis of the aforementioned alcohol (IVb)[15] to give IVc.

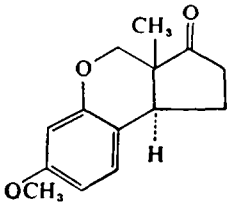
Finally, assignment of structure IVa for the abnormal product resulted from a study of its NMR spectrum which shows peaks at 70 (9H, singlet), 95·5 (3H, singlet), 229 (3H, singlet), 233 (3H, singlet), 217 (2H, multiplet), 390 (2H, multiplet) and 439 c/s (1H, doublet, J = 9 c/s). The presence of a t-butyl moiety in this product was clearly indicated by the signal at 70 c/s with an intensity of nine protons. Cleavage of the chromanone ring was inferred from the two signals occurring at 229 and 233 c/s, expected for methoxyl groups on an aromatic ring. The signals at 390 and 439 c/s indicate the 1, 2, 4-substitution pattern of the aromatic ring.[4] Further evidence for the presence of the t-butyl moiety in this product was obtained from its IR spectral characteristics. The bands at 1379 and 1364 cm^{-1}, the intensity of the latter being more than that of the former is characteristic of the t-butyl group.[16] The bands at 1174, 1022, 900, 813 and 758 cm^{-1} are also indicative of a t-butoxy group.[17]

With a view to providing chemical evidence for the presence of the t-butoxy moiety, the abnormal product (IVa) was treated with trifluoroacetic acid according to the procedure of Beyerman *et al.*[18] The crude product, thus obtained, shows the presence of hydroxyl (3636 cm^{-1}), trifluoroacetate (1792 cm^{-1}) and conjugated ketone (1681 cm^{-1}), and also the absence of a t-butoxy group in the IR spectrum. Further purification to obtain IVd could not be achieved as the trifluoroacetate moiety was partially removed on chromatography. Such an observation has recently been made by Beyerman *et al.*[19] However, treatment of IVa with glacial acetic acid containing perchloric acid furnished the acetate (IVe) as proved by its IR spectrum.

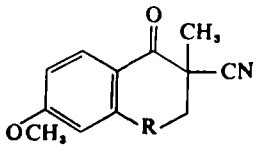
The probable mechanism for the formation of IVa during the isomerization of III followed by methylation is shown in Chart I.

The initially formed anion (VI) could undergo a β-elimination[20] followed by

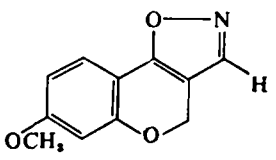
[12] W. N. Speckamp, U. K. Pandit and H. O. Huisman, *Rec. Trav. Chim.* **82**, 39 (1963).
[13] M. K. Bhattacharjee, R. B. Mitra, B. D. Tilak and M. R. Venkiteswaran, *Tetrahedron* **10**, 215 (1960).
[14] G. Subrahmanyam, Ph.D. Thesis of Jadavpur University, India, p. 36 (1962); D. K. Banerjee and G. Subrahmanyam. Unpublished work.
[15] Under similar conditions, hydrogenolysis of the parent ketone (IVa) was very sluggish.
[16] C. N. R. Rao, *The Chemical Applications of Infrared Spectroscopy* p. 139, Academic Press, New York (1963).
[17] H. A. Ory, *Analyt. Chem.* **32**, 509 (1960).
[18] H. C. Beyerman and J. S. Bontekoe, *Rec. Trav. Chim.* **82**, 691 (1962).
[19] H. C. Beyerman and G. J. Heiszwolf, *Rec. Trav. Chim.* **84**, 203 (1965).
[20] Similar β-elimination resulting in the cleavage of the chromanone ring after prolonged refluxing with sodium ethoxide in ethanol is also recorded.[10]



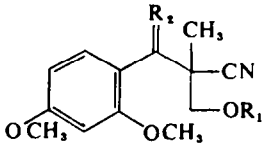
I

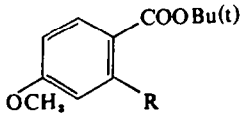


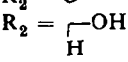
IIa, R = O
b, R = NTs



III





IV a, $R_1 = C(CH_3)_3$; $R_2 = O$
b, $R_1 = C(CH_3)_3$; $R_2 =$ 
c, $R_1 = C(CH_3)_3$; $R_2 = H_2$
d, $R_1 = COCF_3$; $R_2 = O$
e, $R_1 = COCH_3$; $R_2 = O$

Va, R = NHTs

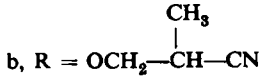
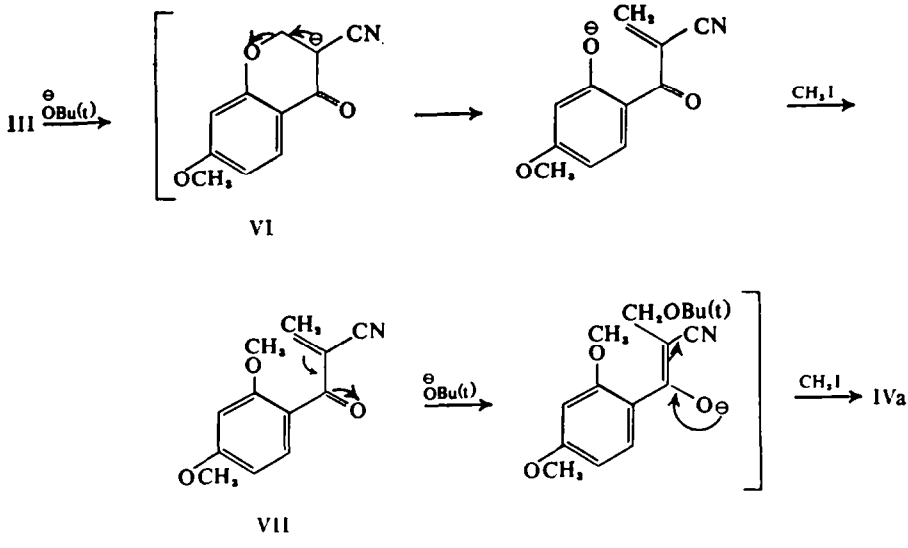
b, R = 

CHART 1



VI

VII

methylation to give VII. Michael addition of the t-butoxide anion[21,22] to the highly resonance stabilized species (VII) followed by methylation could lead to IVa. Such an "abnormal" reaction was not noticed when alkoxides like sodium methoxide in methanol, sodium ethoxide in ethanol and even potassium isopropoxide in isopropanol

[21] C. E. Rehberg, Marion B. Dixon and C. H. Fisher, *J. Amer. Chem. Soc.* **68**, 544 (1946).
[22] J. H. McGregor and C. Pugh, *J. Chem. Soc.* 535 (1945). See also H. Bruson, *Organic Reactions* Vol. V, p. 79. J. Wiley, New York (1949).

were employed in the above isomerization reaction.[23] However, the expected cyanomethyl ketone (IIa) was obtained in very poor yield.

Considering that the excess of potassium t-butoxide used in the foregoing isomerization experiment could lead to the formation of IVa, an inverse addition of only 1·2 moles of potassium t-butoxide to a stirred suspension of III in t-butanol containing a fairly large excess of methyl iodide was carried out to yield the desired[24] cyanomethyl ketone (IIa) in 45% yield. This reaction using similar molar proportions of sodium methoxide and sodium ethoxide, gave IIa, sodium ethoxide in ethanol furnishing the better yield (60%). The structure of IIa was proved beyond doubt by its UV [λ_{max} 235 (ε 9520), 278 (14,410) and 310 mμ (8065)], IR [(Nujol) 2262 (C≡N), 1689 (conjugated C=O), 1613, 1567 (aromatic C=C), 1035, 1024, and 834 cm^{-1} (1,2,4-trisubstituted benzene)] and NMR spectra. The signals at 96·5 (3H, CH_3), 267 (2H, quartet, J = 12 c/s, —O—CH_2—) and 231 c/s (3H, —OCH_3) are in conformity with structure IIa. Further, the doublet centred at 469 c/s (J = 9 c/s, C_5 proton coupled with C_6 proton), the doublet centred at 387 c/s (J = 2·5 c/s, C_8 proton coupled with C_6 proton) and a pair of doublets centred at 398·5 c/s (C_6 proton split by C_5 and C_8 protons, $J_{6,5}$ = 9 c/s and $J_{6,8}$ = 2·5 c/s) are indicative of 1,2,4-substitution pattern of the aromatic ring.[4]

Attempts to convert IIa to the key intermediate (I) are in progress.

EXPERIMENTAL*

General. All m.ps are uncorrected. UV spectra were determined in 95% EtOH (unless otherwise specified) using a Beckmann DU Spectrophotometer. IR spectra were recorded with a Perkin–Elmer Model 137 B Infracord Spectrophotometer. NMR spectra were measured in $CDCl_3$ solution on a Varian A-60 Spectrometer; chemical shifts are quoted in c/s units at 60 Mc/s downfield from tetramethylsilane as internal standard. Pet. ether b.p. 40–60° only was used. Microanalyses were carried out by Messrs. B. R. Seetharamia and H. S. Thyagarajan of this department.

3-*Formyl-7-methoxychroman-4-one*

A solution of 7-methoxychroman-4-one (20 g) in dry benzene (300 ml) was added at 15° to a mixture of dry MeONa (from 7·6 g Na), ethyl formate (20 ml) and benzene (50 ml) in an atmosphere of N_2. The mixture was stirred for 1 hr at 15–20° and for 5 more hr at room temp. The pale orange reaction mixture was diluted with water, and the benzene solution extracted with 5% NaOHaq. The combined water and alkaline extracts, after cooling, were acidified with ice-cold conc. HCl and the precipitate filtered, washed and dried. The sticky solid (22 g, 95%) on crystallization from aqueous EtOH gave pale yellow leaflets, m.p. 96–97°. (Found: C, 64·07; H, 4·86. $C_{11}H_{10}O_4$ requires: C, 64·08; H, 4·85%.) UV λ_{max} 230 (ε 11,580), 250 (7470), 274 (11,400), 305 (7140) and 355 mμ (9470). IR ($CHCl_3$) peaks at 3356 (bonded —OH), 1681 (conjugated C=O) and 1639 cm^{-1} (chelated conjugated C=O).

7-*Methoxychromano*-(4,3-d)-*isoxazole* (III)

A solution of the foregoing formyl compound (10·5 g) in glacial acetic acid (240 ml) was treated with dry, powdered hydroxylamine hydrochloride (2·9 g) and the mixture quickly heated to boiling in an oil-bath maintained at 170°. Refluxing was continued for 7 min and then hot water was added until the pink solution became turbid. The contents were cooled and left overnight in the refrigerator. The mixture was extracted with benzene, washed with water, cold 5% NaOHaq and then several times

* We are thankful to Mr. B. L. Mylari for some of the preliminary experiments in this series.

[23] Further work is being carried out to throw more light on the mechanism.

[24] The nature of the other products obtained in this reaction is under further investigation.

with water. The solvent was distilled off to give a pale yellow solid (8·3 g, 80%). One crystallization from EtOH afforded pale yellow needles, m.p. 95–96°. (Found: N, 7·16; C, 65·6; H, 4·63. $C_{11}H_9NO_3$ requires: N, 6·9; C, 65·03; H, 4·43%.)

Treatment of isoxazole (III) *with alkoxides and methyl iodide using Johnson's conditions*[8]

(a) *Potassium t-butoxide in t-butanol.* Compound III (1·08 g) was added to a solution of K (0·68 g) in t-butanol (20 ml). The orange suspension of the potassium derivative was heated with stirring at 75–80° (10 min) when a clear orange solution was obtained; and then MeI (7 ml) was added dropwise (10 min) with continued stirring and heating under reflux which was continued for an additional 20 min. The unreacted MeI and the solvent were removed *in vacuo*, water was added and the mixture extracted with benzene. The benzene solution was washed successively with cold 5% KOHaq, water, cold dil. HClaq and then several times with water. The residue (1·19 g) obtained after removal of the solvent was chromatographed on activated alumina to give three fractions:-

Fraction I. (1:1 pet. ether–benzene mixture, 0·72 g), crystallized from pet. ether containing a few drops of benzene, m.p. 77–78°. (Found: N, 4·44; C, 67·15; H, 7·82. $C_{17}H_{23}NO_4$ requires: N, 4·59; C, 66·84; H, 7·54%); identified as IVa.

Fraction II. (Benzene–ether mixture, 0·2 g), a fluorescent yellow oil having peaks in the IR (smear) at 2222 (conjugated —C≡N), 1678 (conjugated C=O), 1608 and 1582 cm^{-1} (aromatic C=C).

Fraction III. (MeOH, 0·2 g), crystallized from MeOH in shining white plates, m.p. 150–152°. UV λ_{max} 234, 274 and 308 mμ. IR ($CHCl_3$) 1681 (conjugated C=O), 1639, 1608 and 1582 cm^{-1} (aromatic C=C).

(b) *Sodium methoxide in methanol.* Compound III (500 mg) was added to a solution of Na (185 mg) in dry MeOH (12 ml) and then treated with MeI (4 ml) according to the experimental conditions given under (a). The crude neutral product was chromatographed and two fractions were collected:

Fraction I (1:1 pet. ether–benzene, 55 mg), crystallized from pet. ether–CCl_4, m.p. 91–92° and identified as IIa. (Found: N, 6·81; C, 66·7; H, 5·25; $C_{12}H_{11}NO_3$ requires: N, 6·45; C, 66·35; H, 5·25%.)

Fraction II. (MeOH, 215 mg). Repeated crystallization from EtOH gave a pale yellow solid, m.p. 174–175°. UV λ_{max} 249, 276 and 305 mμ. IR (Nujol) 1672 (conjugated C=O), 1637, 1608 and 1582 cm^{-1} (aromatic C=C).

(c) *Sodium ethoxide in ethanol.* Experiment (b) was repeated with the isoxazole (300 mg), Na (111 mg), EtOH (12 ml) and MeI (3 ml) when IIa (47 mg) and fraction II (44 mg) of experiment IIIb were obtained.

(d) *Potassium isopropoxide in isopropanol.* From III (300 mg), K (195 mg), isopropanol (12 ml) and MeI (3 ml), IIa (153 mg) and fraction II (100 mg) of experiment IIIb were obtained.

Treatment of isoxazole with alkoxides and methyl iodide under modified condition

(a) *Potassium t-butoxide in t-butanol.* To a stirred suspension of III (300 mg) in t-butanol (10 ml) containing MeI (0·5 ml), a solution of K (72 mg) in t-butanol (5 ml) was added dropwise and the stirring continued for 5 hr. The solvent was removed *in vacuo*, water added and the mixture extracted with benzene. The extract was washed with 5% NaOHaq, water, dil. HClaq and water respectively. The residue obtained after removal of solvent was chromatographed to yield two fractions:

Fraction I. (1:1 pet. ether–benzene, 140 mg), crystallized from pet. ether–CCl_4, m.p. 91–92° and identified as IIa.

Fraction II. (MeOH, 48 mg), crystallized from EtOH, m.p. 173–175°, identical with fraction II of aforementioned experiment (IIIb).

(b) *Sodium methoxide.* Experiment (a) was repeated with III (300 mg), Na (41 mg), MeOH (15 ml) and MeI (0·5 ml) when IIa (142 mg) and fraction II (85 mg) of experiment IIIb were obtained.

(c) *Sodium ethoxide.* From III (300 mg), Na (41 mg), EtOH (15 ml) and MeI (0·5 ml), IIa (195 mg) and fraction II (75 mg) of experiment IIIb were obtained.

Sodium borohydride reduction of IVa

3-t-Butoxy-2-cyano-1-hydroxy-2-methyl-2′,4′-dimethoxypropylbenzene (IVb). A solution of IVa (100 mg) and $NaBH_4$ (13 mg) in dry EtOH (10 ml) was stirred for 1 hr, EtOH removed *in vacuo* and water added. The organic material was extracted with ether, the extract washed with water and dried (Na_2SO_4). The solvent was removed and the residual oil (100 mg) purified by short-path distillation,

b.p. 130–140°/1–2 mm. (Found: N, 5·09; C, 66·56; H, 8·45. $C_{17}H_{25}NO_4$ requires: N, 4·56; C, 66·42; H, 8·20%.) UV λ_{max} 230 (ε 8190) and 278 mμ (2400). IR (smear) 3636 (—OH), 2273 (—C≡N) 1613, 1587 (aromatic C=C), 1389, 1361 (—*t*Bu), 1190, 1031, 962, 833 and 761 cm^{-1} (*t*-BuO).

Hydrogenolysis of IVb

3-*t-butoxy-2-cyano-2-methyl-2′,4′-dimethoxypropylbenzene* (IVc). A solution of IVb (350 mg) in ethyl acetate (25 ml) containing a trace of 70% $HClO_4$ was stirred with 30% Pd–C catalyst (350 mg) in an atmosphere of H_2 until no more H_2 was absorbed. The solution was filtered, washed with 5% $NaHCO_3$aq and water. The residue obtained after removal of solvent was purified by chromatography over neutral alumina. The pet. ether fraction (95 mg) was further purified by preparative TLC and an analytically pure sample obtained by short-path distillation, b.p. 140°/1–2 mm. (Found: N, 4·31; C, 69·61; H, 9·00. $C_{17}H_{25}NO_3$ requires: N, 4·81; C, 70·09; H, 8·59%.) UV[25] λ_{max} 230 (ε 8695), 278 (2625) and 284 mμ (2405). IR (smear) 2273 (—C≡N), 1613, 1587 (aromatic C=C), 1389, 1361 t-Bu), 1190, 1031, 880, 833 and 766 cm^{-1} (t-BuO).

Action of perchloric acid and acetic acid on IVa

3-*Acetoxy-2-cyano-2-methyl-2′,4′-dimethoxypropiophenone* (IVe). A solution of IVa (300 mg) in glacial acetic acid (10 ml) containing 70% $HClO_4$ (1 ml) was stirred at room temp for 24 hr. The solution was then diluted with water, neutralized with solid $NaHCO_3$, extracted with ether, washed with water and dried (Na_2SO_4). The residue, obtained after removal of the solvent, was chromatographed over neutral alumina. The benzene fraction (165 mg) was further purified by preparative TLC and short-path distillation, b.p. 140–150°/1–2 mm. (Found: N, 5·01. $C_{15}H_{17}NO_5$ requires: N, 4·81%.) UV λ_{max} 234 (ε 9955), 273 (8595) and 305 mμ (6225). IR (smear) 2273 (—C≡N), 1754 (ester C=O), 1678 (conjugated C=O), 1608, 1582 (aromatic C=C), 1504 and 1260 cm^{-1} (acetate).

Acknowledgements—The authors are thankful to Professor D. K. Banerjee for his kind suggestions and helpful discussions. We are grateful to Dr. M. Nagabhushanam, Oklahoma State University, Stillwater and Mr. B. L. Mylari, Indiana University, Bloomington for their help in taking the NMR spectra reported here. Our thanks are particularly due to Dr. S. R. Ramadas of our department and Mr. B. L. Mylari for useful discussions.

One of us (K. M. D.) is thankful to the Indian Institute of Science for the award of a pre-doctoral fellowship.

[25] UV spectrum was measured in cyclohexane.