A Novel Preparation of Isonitriles[1]

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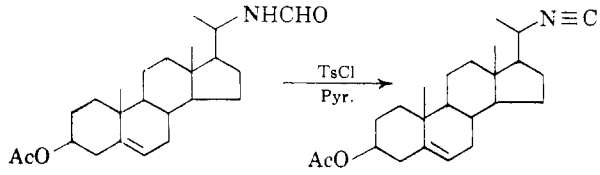
In connection with other studies it was found that a formamide which was treated with *p*-toluenesulfonyl chloride and pyridine was dehydrated to an isonitrile according to the equation

$$R{-}NHC(H){=}O + 2C_5H_5N + ArSO_2Cl \longrightarrow R{-}N{\equiv}C + 2C_5H_5N\overset{+}{H} + ArSO_3^- + Cl^-$$

The reaction appears to be quite general as is indicated by three diverse examples described herein from the aliphatic, alicyclic, and aromatic series. The practicality of the new method is obvious both from the ready availability of the required formamides and the simplicity of the procedure involved (see Experimental). The previously known general routes to isocyanides[2] involve (1) reaction of silver cyanide with alkyl halides and (2) reaction of primary amines with chloroform and alkali. It had previously been observed that pyrolysis of formamides gives trace amounts of isonitriles.[3]

When *N*-formyl-*p*-xylidine was treated with excess *p*-toluenesulfonyl chloride in pyridine a green color developed, and a 50% yield of 2,5-dimethylbenzoisonitrile was obtained after distillation. Similarly, 3β-acetoxy-20α-formamidopregnene-5 was converted to 3β-acetoxy-20α-isocyanopregnene-5 in 84% yield. The alicyclic formamide, 3α-formamidocholestane, was likewise dehydrated to 3β-isocyanocholestane in 93% yield.



The infrared absorption spectra of each of these isonitriles displayed a characteristic strong band at 2120–2140 cm.$^{-1}$

EXPERIMENTAL[4]

2,5-Dimethylbenzoisonitrile. *N*-Formyl-*p*-xylidine (7.46 g., 0.05 mole) and 13.3 g. (0.07 mole) of *p*-toluenesulfonyl chloride were dissolved in 40 ml. of pyridine, and the resulting orange-red solution was allowed to stand at room temperature. After one hour the solution had become green, and after 1.5 hr. the solution was cooled and treated with chipped ice and then poured into ice water. The product was extracted with ether, and the ethereal solution was washed three times with cold water and then dried over sodium sulfate. Most of the solvent was removed at atmospheric pressure, and the residue was distilled through a 20-cm. Holzmann column to give 3.305 g. (50%) of 2,5-dimethylbenzoisonitrile, b.p. 87.5–90° at 12 mm. (lit.,[5] b.p. 79–82° at 20 mm., 99° at 32 mm.).

3β-Acetoxy-20α-formamidopregnene-5. Acetoxybisnorcholenic acid (50 g.) was converted to a 3β-acetoxy-20α-aminopregnene-5 acetate by the procedure of Julian,[6] and the crude acetate was refluxed with 130 ml. of formic acid (98–100%) and 110 ml. of acetic anhydride for 5 hr. Then the solution was diluted with ice water and extracted with methylene chloride. The organic layer was washed with water and dried over sodium sulfate. The solvent was removed *in vacuo* leaving a tan residue which on crystallization from acetone gave 37.6 g. (75%) white amorphous solid, m.p. 191–195°. Repeated crystallization from acetone gave fine needles, m.p. 191–193°, $[\alpha]_D^{16}$ −66° (chf., c, 2.8).

Anal. Calcd. for $C_{24}H_{37}NO_3$: C, 74.38: H, 9.63. Found: C, 74.32; H, 9.87.

3β-Acetoxy-20α-isocyanopregnene-5. 3β-Acetoxy-20α-formamidopregnene-5 (150 mg., 0.387 mmole.) was dissolved in 2.5 ml. of pyridine, and to this was added 95 mg. (0.5 mmole.) of *p*-toluenesulfonyl chloride. After standing for 1.5 hr. at room temperature the solution was treated with a few chips of ice and poured into ice water. The product was extracted with ether-pentane, washed with water, and dried over sodium sulfate. Evaporation of the solvent gave a white crystalline residue which on crystallization from hexane gave 119.3 mg. (84%) of 3β-acetoxy-20α-isocyanopregnene-5, m.p. 144–151°. Further crystallization from hexane gave prismatic needles, m.p. 149–150°, $[\alpha]_D^{16}$ −48° (chf., c, 1.2).

Anal. Calcd. for $C_{24}H_{35}NO_2$: C, 78.00; H, 9.55. Found: C, 78.11; H, 9.62.

3α-Formamidocholestane. The following procedure was used for the preparation of 3α-aminocholestane and was found to give a purer product than the published methods:[7,8] Cholestanyl *p*-toluenesulfonate (11.28 g., 20.8 mmole.) was added in one portion to a stirred slurry of 40 g. of sodium azide in 300 ml. of dry dimethylsulfoxide, and the mixture was heated at 83–84° with stirring for 5.5 hr. The mixture was cooled, poured into ice water, and extracted with ether-pentane. The organic layer was washed three times with water and dried over sodium sulfate. Removal of solvent *in vacuo* gave a sirupy residue which was dissolved in 190 ml. of dry ether, and to this was added 3.6 g. of lithium aluminum hydride. The resulting slurry was stirred at room temperature for 11 hr. and then cautiously treated with water. The precipitate was removed and washed with ether. The combined washings and filtrate were dried over sodium sulfate. Dry hydrogen chloride was passed into the ethereal solution, and the precipitated amine hydrochloride was filtered off and washed thoroughly with ether. The filter cake, which weighed 7 g., was stirred for 0.5 hr. with concentrated ammonium hydroxide and pentane. The pentane layer was separated and dried over sodium sulfate. The solvent was evaporated, and the white crystalline residue was recrystallized from methanol to give 5.263 g. (65%) of 3α-aminocholestane, m.p. 104.5–105.5°, $[\alpha]_D^{16}$ 27° (chf., c, 1.1), (lit., m.p. 87–88°,[7] 89°,[8] $[\alpha]_D$ 27°).[7]

Anal. Calcd. for $C_{27}H_{49}N$: C, 83.65; H, 12.74; N, 3.61. Found: C, 83.59; H, 12.90; N, 3.61.

(1) This investigation was supported by fellowship AF-7544 from the National Institute of Arthritis and Metabolic Diseases, Public Health Service.

(2) J. Houben, *Die Methoden der Org. Chem.*, 3rd ed. Georg Thieme, Liepzig, 1941, vol. 4, p. 29.

(3) J. U. Nef, *Ann.*, **270**, 267 (1892).

(4) All melting points are corrected, and boiling points are uncorrected.

(5) J. Ploquin, *Bull. soc. chim. France*, 901 (1947).

(6) P. L. Julian, E. W. Meyer, and H. C. Printy, *J. Am. Chem. Soc.*, **70**, 887 (1948).

(7) C. W. Shoppee, D. E. Evans, H. C. Richards, and G. H. R. Summers, *J. Chem. Soc.*, 1649 (1956).

(8) L. Labler, V. Czerny, and F. Sorm, *Chem. listy*, **48**, 1058 (1954).

3α-Aminocholestane (2 g., 5.16 mmole.) was refluxed with 15 ml. of formic acid and 10 ml. of acetic anhydride for 12 hr. The solution was cooled, diluted with water, treated with about one half equivalent of 10% sodium hydroxide solution, and extracted with methylene chloride. The methylene chloride solution was washed with water and dried over sodium sulfate. Removal of solvent and crystallization of the residue from acetone gave 1.842 g. (86%) of feathery needles, m.p. 179–181°. Repeated crystallization from acetone gave 3α-formamidocholestane, m.p. 188–189°, $[\alpha]_D^{1.6}$ 35.6° (chf., c, 2.2).

Anal. Calcd. for $C_{28}H_{49}NO$: C, 80.90; H, 11.88; N, 3.37. Found: C, 81.02; H, 11.82; N, 3.27.

3α-Isocyanocholestane. 3α-Formamidocholestane (500 mg., 1.2 mmole.) was covered with 10 ml. of dry pyridine, and 382 mg. (2 mmole.) *p*-toluenesulfonyl chloride was added. The resulting orange solution was allowed to stand for 1.5 hr. at room temperature, cooled, treated with ice, and poured into ice water. The product was extracted with ether, washed twice with water, and dried over sodium sulfate. Removal of solvent and crystallization of the pink residue from acetone gave 442.6 mg. (93%) of flat needles, m.p. 139–141°. Further crystallization from acetone gave 3α-isocyanocholestane, m.p. 141–143°, $[\alpha]_D^{1.6}$ 27° (chf., c, 1.6).

Anal. Calcd. for $C_{28}H_{47}N$: C, 84.56; H, 11.91; N, 3.53. Found: C, 84.67; H, 11.89; N, 3.47.

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Action of Primary Aliphatic Amines on 2-Methyl-1,4-α-naphthopyrone

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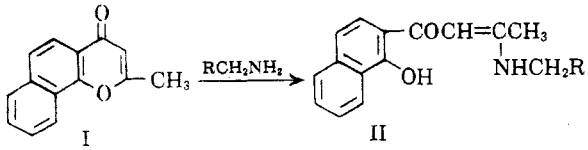
The action of alcoholic ammonia on 2-methyl-1,4-α-naphthopyrone has been studied by Wittig and Blumenthal.[1] Recently Musante and Stener[2] have studied the action of primary aliphatic amines on the 2-methylchromone derivative Khellin. Both groups of researchers agree that the reaction products are 2-(β-aminocrotonyl)phenols (type II).

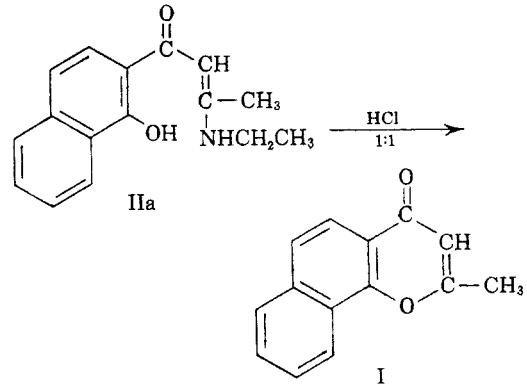
The author has investigated the action of ethylamine, butylamine, and benzylamine on 2-methyl-1,4-α-naphthopyrone(I), and believes that the reaction products are the 2-(β-aminocrotonyl)-1-naphthol derivatives IIa, IIb, and IIc.



I II

a: R = CH_3
b: R = $CH_2CH_2CH_3$
c: R = C_6H_5

The alcoholic solution of these substances gives a green color with alcoholic ferric chloride solution. This fact indicates that they contain a free phenolic hydroxyl group. When IIa was refluxed with dilute hydrochloric acid (1:1), 2-methyl-1,4-α-naphthopyrone (I) was obtained on cooling. The hydrolysis of IIb with aqueous alkali yielded 1-hydroxy-2-naphthoic acid.



EXPERIMENTAL

2-(β-Ethylaminocrotonyl)-1-naphthol IIa. 2-Methyl-1,4-α-naphthopyrone[3] (2 g.) was heated under reflux with two ml. of ethylamine solution in 20 ml. of ethyl alcohol on a steam bath for 3 hr. The deep yellow crystalline solid that precipitated on cooling was filtered off and crystallized from petroleum ether (b.p. 80–100°); m.p. 126°; yield 1.9 g. It has a green fluorescence and is insoluble in aqueous sodium hydroxide solution (10%). It gives a green color with alcoholic ferric chloride solution and a red color with concentrated sulfuric acid.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7; N, 5.5. Found: C, 75.2; H, 6.7; N, 5.4.

2-(β-Butylaminocrotonyl)-1-naphthol IIb was obtained from 2-methyl-1,4-α-naphthopyrone (2 g.) and butylamine (2 ml.). This compound was crystallized from petroleum ether (b.p. 80–100°) as deep yellow crystals with green fluorescence, m.p. 106°; yield 1.8 g. It dissolved in concentrated sulfuric acid with an orange color and was insoluble in cold alkali. Its alcoholic solution gave a color reaction with ferric chloride solution (deep green).

Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.3; H, 7.4; N, 5.0. Found: C, 76.6; H, 7.5; N, 4.8.

2-(β-Benzylaminocrotonyl)-1-naphthol IIc. The same procedure was followed with benzylamine. This compound was crystallized from petroleum ether (b.p. 80–100°), as deep yellow crystals with green fluorescence, m.p. 136°; yield 80%. It gives a red-orange color on treatment with concentrated sulfuric acid and a deep green color with ferric chloride solution.

Anal. Calcd. for $C_{21}H_{19}NO_2$: C, 79.5; H, 6.0; N, 4.4. Found: C, 79.6; H, 6.1; N, 4.5.

Action of hydrochloric acid on IIa. Half a gram of IIa was heated under reflux with 25 ml. of dilute hydrochloric acid (1:1) for 0.5 hr. The colorless crystalline solid that separated on cooling was filtered off and proved, by melting point and mixture melting point (178°), and the deep violet color reaction[4] on adding alkali to its solution in dioxane containing *m*-dinitrobenzene, to be 2-methyl-1,4-α-naphthopyrone.

Hydrolysis of IIb *with alkali.* IIb (0.5 g.) and aqueous sodium hydroxide solution (5%, 25 ml.) was heated under reflux for 2 hr. The filtrate was acidified with dilute hydro-

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(2) C. Musante and A. Stener, *Gazz. chim. ital.*, **86**, 297 (1956).
(3) G. Wittig, Fr. Bengert, and H. E. Richter, *Ann.*, **446**, 155 (1926).
(4) A. Schönberg and M. M. Sidky, *J. Org. Chem.*, **21**, 476 (1956).