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A NEW SYNTHESIS OF THEASPIRONE, AN ODIFEROUS PRINCIPLE OF TEA[1]

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Abstract—A new synthesis of theaspirone (**10**) is recorded. The key step involves coupling between the organolithium reagent **6**, derived from 4-bromo-2-butanol (**4**), and the monoketal of 4-ketoisophorone (**3**). Removal of protecting groups and ether cyclization then gave theaspirone **10** and its diastereoisomer **11**.

Theaspirone, one of two compounds responsible for the odor of black tea, has been shown to have structure X by Ina *et al.*,[2] although is stereochemistry was not determined. Very recently, it was shown to have the S,S absolute stereochemistry.[3] This reverses an earlier assignment.[4]

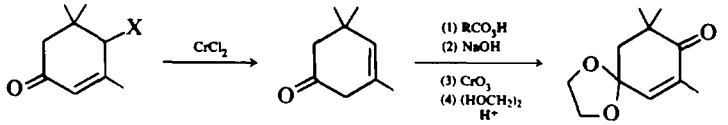
Several syntheses of racemic theaspirone have been recorded[5-7] and one has been modified to allow a resolution step.[3] These synthetic routes have all proceeded from ionone precursors, which contain the complete carbon skeleton of theaspirone. This paper describes a different approach, in which the spiro ether ring is built onto a key intermediate (**3**) derived from isophorone (**1a**).

The monoketal of 4-ketisophorone (**3**) has been synthesized previously from β-phorone (**2**).[8] However, much difficulty was experienced in repeating the methyl magnesium bromide-catalyzed deconjugation of isophorone[9] to obtain β-phorone. A new route to this important intermediate[10] was therefore developed.[11] This involved the reductive deconjugation of 4-bromoisophorone (**1b**) with $CrCl_2$ or $Cr(OAc)_2$.[11] Other syntheses of β-phorone have also appeared recently,[12,13] but this method appears to be the most reproducible and the most convenient, at least on a small or medium size scale.

To construct the theaspirone skeleton, it was decided to add the functionalized four carbon fragment via an organometallic reagent. Since the ketone **3** is subject to quite a bit of steric hindrance, the organolithium reagent **6**, which was expected to have great reactivity and relatively small steric requirements, was chosen.

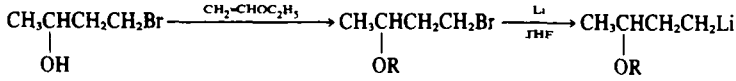
Addition of HBr gas to neat methyl vinyl ketone[14] proceeded without polymerization when the reaction was carried out at low temperature and any excess of HBr was avoided. The resulting 4-bromo-2-butanone was then reduced with $NaBH_4$ at 0° to give 4-bromo-2-butanol (**4**)[14] in 85% overall yield. Reaction of this with ethyl vinyl ether was instantaneous without added catalyst. This gave a mixture of the acetaldehyde acetals **5a** and **5b**. The mixed acetaldehyde acetal of 4-bromo-2-butanol and ethanol (**5a**) could be obtained pure (as a diastereoisomeric mixture) by distillation (54% yield) but it reverted to the equilibrium mixture overnight. This acetal exchange may be catalyzed by traces of HBr in the product. The higher-boiling diacetal **3b**, again as a diastereoisomeric mixture (40%), was stable to storage. Either **5a** or **5b** was suitable for further reactions.

Treatment of **5** with Li in THF gave the rather unstable lithium compound **6**, which tended to abstract a proton from some source and give the acetal of 2-butanol. The tetrahydropyranyl ether of 4-bromo-2-butanol, prepared in the usual manner from dihydropyran, was found to give an even more unstable organolithium derivative. However the organolithium reagent **6** could be effectively trapped by generating it in the presence of the ketone **3**. This procedure gave the adduct **7** as a diastereoisomeric mix-



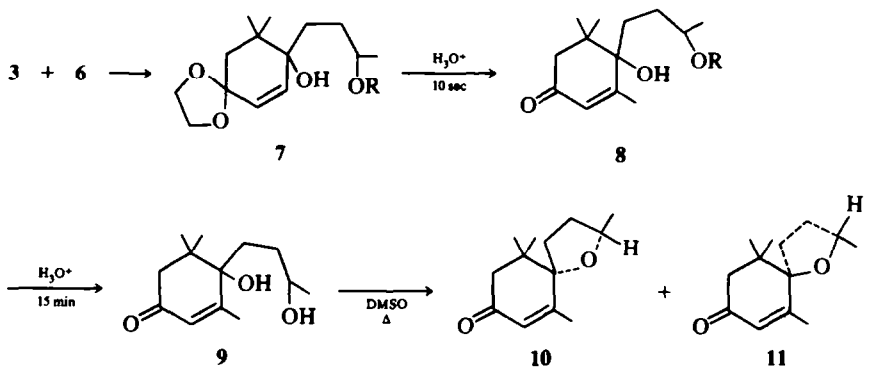
1a: X = H
b: X = Br

2 **3**



4 **5** **6**

a: R = $-CH(CH_3)-OC_2H_5$; **b**: R = $-CHOCHCH_2CH_2Br$ (CH_3, CH_3)



ture in over 85% yield. Removal of the ethylene ketal grouping was instantaneous in dilute HCl to give **8**, and the ethyl vinyl acetal protecting group was subsequently removed within 15 min, as recommended for a similar case.[15] The resulting product, again as a diastereoisomeric mixture, had the spectral properties reported previously for the diol mixture **9**.[7] Heating this in DMSO gave authentic (±) theaspirone **10** and its diastereoisomer **11**, as reported.[5-7]

The protecting groups of **7** could be removed and the ether cyclization effected by thermal means. This was most conveniently carried out in a gas chromatograph injection port. Thus, injecting samples of **7**, **8**, or **9** into a gas chromatograph (injector at 250°) gave good conversion to theaspirone **10** and its isomer **11**.

EXPERIMENTAL

Synthesis of 4-bromo-2-butanol (**4**)

In a 3-neck flask fitted with a magnetic stirrer, gas inlet tube and mercury bubbler, was placed 53·10 g of methyl vinyl ketone. The flask was cooled to −78° with dry ice–acetone then 43·6 g (0·95 eq) of HBr gas was bubbled in over a period of 3–4 hr. The progress of the reaction was monitored approximately by the loss of weight of the HBr cyclinder and verified by disassembling the flask, stoppering it, allowing it to come to room temp., and weighing it. If the amount of HBr added was more than one equivalent, brown polymer slowly formed when the flask was warmed to room temp. This could be avoided by adding more methyl vinyl ketone to slight excess (conveniently monitored by NMR spectroscopy: δ (neat) 2·24 (3H, sing), 3·13 (2H, triplet), 3·62 (2H, triplet).

The 4-bromo-2-butanone, containing 5% methyl vinyl ketone but no other impurities detectable by NMR spectroscopy, was dissolved in cold MeOH and 10 g of $NaBH_4$ was added in portions with stirring over a 3 hr period at 0–10°, then stirring was continued 1 hr further. Then the mixture was neutralized with HCl, poured into ten volumes of H_2O and extracted three times with ether. The ether soln was washed, dried ($MgSO_4$) and the ether removed to give an oil which was distilled, $b.p._{\cdot 0\,1}$ 50–57°; (lit.[14] $b.p._{14}$ 75–77°) 98·70 g (85%), NMR (CCl_4): δ 1·33 (3H, d, J = 7), 2·08 (2H, q, J = 7), 3·65 (2H, t, J = 7), 4·10 (1H, pentuplet, J = 7), 4·8 (1H, s).

Reaction of ethyl vinyl ether with 4-bromo-2-butanol

Production of **5a** *and* **5b**. To 15·7 g of 4-bromo-2-butanol was added 20 ml ethyl vinyl ether at 0–5° with stirring over a 5 min period. Excess methyl vinyl ether was removed at the aspirator and the residue was distilled at 0·1 mm. Two major fractions were collected: $b.p._{\cdot 0\,1}$ 52–56° (12·34 g, 54%) and $b.p._{\cdot 0\,1}$ 83–87° (6·60 g, 40%). The former fraction turned yellow after standing overnight. Redistillation gave the same two compounds in a similar ratio. The lower boiling one again reverted to the equilibrium mixture overnight. It gave an immediate NMR spectrum as follows: δ 1–1·3 (9H, m), 1·7–2·1 (2H, m), 3·1–4·0 (5H, m), 4·7 (2H, pair of close quartets), which identifies it as **5a**. (Found: C, 42·37; H, 7·47. Calc. for $C_8H_{17}O_2Br$; C, 42·68; H, 7·61%).

The 83–87° fraction was colorless and redistillation gave unchanged material, $b.p._{\cdot 0\,1}$ 84–86°, which was unchanged after several months storage. This material has NMR (CCl_4): δ 1·1–1·4 (9H, m), 1·8–2·2 (4H, m), 3·4–4·0 (6H, m), 4·7 (2H, broadened q). This material was identified as the acetaldehyde diacetal of **5b**. (Found: C, 36·69; H, 6·11. Calc. for $C_{10}H_{20}O_2Br_2$: C, 36·17; H, 6·07%).

Organolithium coupling to produce **7**. A 4 in piece of Li wire (1% Na) (ca. 4 eq) was cut into small pieces dropped directly into 15 ml of dry THF (from LAH) under N_2 in a flamed 3-necked flask which was fitted with a serum cap. Then a soln of 0·26 g of the acetal **5a**, (although **5b** worked equally as well) and 0·15 g of the ketal **3** were added by syringe. The mixture was stirred at room temp. overnight, then poured slowly into ice and water to decompose excess Li. The basic soln was extracted 3 times with ether, the ether washed, dried over $MgSO_4$ and the ether removed to give a viscous oil which was primarily the adduct **7** by NMR: δ (CCl_4): 1·0–1·3 (complex m for Me groups), 1·3–1·8 (complex m), 3·3–3·8 (complex m), 3·9 (4H, s), 4·7 (1H, q), 5·15 (1H, broad s).

Removal of protecting groups

Production of diol **9**. An ether soln of adduct **7** was shaken briefly with 5% HCl. This removed the ketal group completely to give crude **8**: NMR δ (CCl_4): 1·0–1·3 (15H, m), 1·3–1·8 (6H, m), 2·4–2·7 (3H, m), 4·72 (1H, q), 5·87 (1H, broad s); IR ν_{CCl_4}: 3630, 3420 (broad), 1670, 1640 (sh) cm^{-1}.

The material was chromatographed on 15 g of silica gel with light petroleum : ether mixtures of increasing polarity. The desired product was eluted with 3 : 1 ether–light petroleum, yield 110 mg. A center fraction was distilled at 0·1 mm in a capillary tube for analysis. (Found: C, 68·09; H, 10·27. Calc. for $C_{17}H_{30}O_4$: C, 68·42; H, 10·16%).

Stirring either **7** or **8** with 10 ml of 5% HCl in 10 ml of acetone for 15 min at room temp., followed by removal of the acetone at the aspirator and recovery of the product by $CHCl_3$ extraction, gave the diol **9**; NMR ($CDCl_3$): δ 1·03 (3H, s), 1·09 (3H, s), 1·19 (3H, d), 2·05 (3H, broad s), 2·33 (2H, m), 3·75 (1H, m), 5·85 (1H, broad s); IR ν_{CHCl_3}: 3420, 1655, 1620 cm^{-1}; mass *m/e*: 226. The values are essentially the same as the ones reported by Heckman and Roberts.[7]

Synthesis of theaspirone **10**. Injection of either **7**, **8**, or **9** into a gas chromatograph (1/8 in × 40 ft 5% SE-30 on chromosorb W at 200°, injector 250°) gave, as the major products, two compounds in

a 1:1 ratio, with retention times of 19 and 22 min respectively. A small sample of diol 9 was heated in DMSO as reported[5-7] and the product, after ether extraction, showed the same two major components by VPC. The total product from another run of the organolithium coupling reaction was injected onto a 3/8 in × 40 ft SE-30 preparative VPC column at 200°. Both components were collected and the first was identified as theaspirone: IR (film) 1660, 1100 cm^{-1}; mass *m/e* 208, 152; NMR (CCl_4): δ 0·94 (3H, s), 1·08 (3H, s), 1·28 (3H, d, J = 6), 1·98 (3H, d, J = 1·5), 2·28 (2H, s), 4·2 (1H, m), 5·72 (1H, q, J = 1·5). The second component had very similar spectral values and corresponds to the diastereoisomer (11), "*Trans*-Theaspirone".

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