365. *The Morphine–Thebaine Group of Alkaloids. Part VI.* The Condensation of Thebaine with Dienophils.*

By K. W. Bentley and A. F. Thomas.

In a search for new analgesics the thebaine–*p*-benzoquinone adduct has been reduced to a dihydro-derivative, which is as active an analgesic in rats as pethidine. The thebaine–maleic anhydride adduct has been converted into the ester, and the latter reduced with lithium aluminium hydride to the corresponding diol. Condensation of thebaine with 1 : 2- and 1 : 4-naphthaquinone has been studied. Attempts to prepare adducts of β-ethylthiocodide failed.

Thebaine (I), pharmaceutically valueless, can be converted by condensation with dienophils into substances having the basic structure of codeine methyl ether, *e.g.*, thebaine–*p*-benzoquinone (II) and the thebaine–maleic anhydride adduct (III) (Sandermann;[1] Schöpf, von Gottberg, and Petri[2]). These compounds and their derivatives have now been tested for analgesic properties and their behaviour towards hot acids has been studied in relation to the transformation of the thebaine–quinol adduct (IV) into flavothebaone.[2]

Catalytic reduction of the *p*-benzoquinone adduct (II) afforded the 5′ : 6′-dihydro-derivative (V) whose structure was proved by failure of the product to undergo isomerisation by acid to a quinol derivative analogous to the quinol adduct (IV) and by the infrared spectrum (p. 1865). Attempts to reduce the ethylenic bridge of the dihydro-compound (V) failed and examination of a model showed that this bridge is so screened by the other parts of the molecule that adsorption on a catalyst would be very difficult. Demethylation of the dihydro-compound (V) by concentrated hydriodic acid or pyridine hydrochloride has so far not yielded pure material.

Only the keto-alcohol (VI) was obtained by reduction of the diketone (V) with sodium

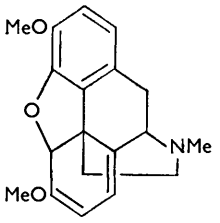
* Part V, *J.*, 1955, 3252.

[1] Sandermann, *Ber.*, 1938, **71**, 648.

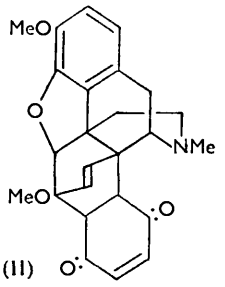
[2] Schöpf, von Gottberg, and Petri, *Annalen*, 1938, **536**, 216.

borohydride; even when an excess was used, reduction of the least hindered of the two carbonyl groups is assumed.

In agreement with the findings of Schöpf, von Gottberg, and Petri [2] we have been unable to hydrogenate either the maleic anhydride adduct (III) or the diethyl maleate adduct (VII;



(I)



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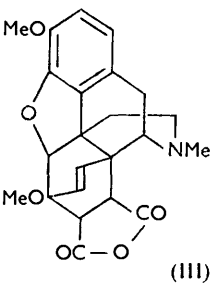

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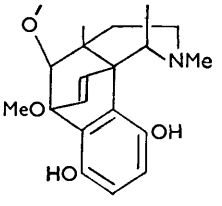

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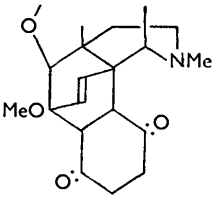

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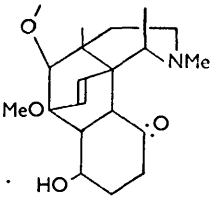
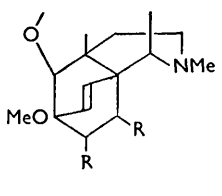


(VI)

R = CO_2Et); the latter was, however, reduced by lithium aluminium hydride to the but-2-ene-1 : 4-diol " adduct " (VII, R = CH_2·OH) (we are aware that this compound would very probably not be formed by the direct addition of but-2-ene-1 : 4-diol to thebaine, but the name used seems the most suitable in absence of fully systematic nomenclature). No rearrangement occurred when the maleic anhydride adduct was heated with concentrated hydrochloric acid or phosphoric acid, the product being the acid, which was identified by conversion into the ester (VII; R = CO_2Et).

A diastereoisomer of the ester (VII; R = CO_2Et), the fumarate adduct, was prepared by condensing thebaine with fumaryl chloride and esterifying the product, but the yields of ester obtained in different experiments varied enormously and the investigation was not pursued.

Condensation of thebaine with 1 : 4-naphthaquinone was reported by Sandermann [1] to give a colourless substance; this condensation could not be repeated according to Sandermann's directions, but treatment of the reaction mixture with acetic acid resulted in the



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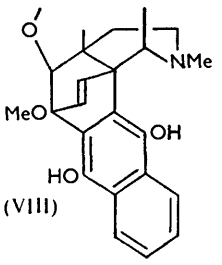

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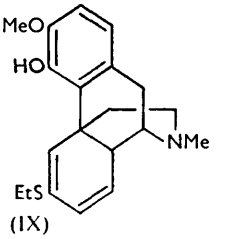

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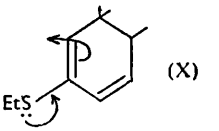

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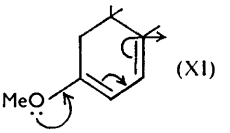

(XI)

subsequent isolation of what is very probably the quinol isomer (VIII) of the initial condensation product. As in the thebaine–*p*-benzoquinone series [3] no methiodide could be prepared from the thebaine–1 : 4-naphthaquinone adduct, but 1 : 4-naphthaquinone and

[3] Bentley, Robinson, and Wain, *J.*, 1952, 958.

thebaine methiodide afforded a methiodide (orange, therefore presumably of the diketone form) which decomposed on recrystallisation, with regeneration of thebaine methiodide. Attempts under a variety of conditions to effect addition of thebaine to the less reactive 1 : 2-naphthaquinone failed.

It was therefore thought possible that β-ethylthiocodide (IX), which also contains a cyclic diene system, might give an adduct with *p*-benzoquinone, but attempts to bring this about failed, probably because only one double bond is activated by the EtS group in β-ethylthiocodide (X) and not the whole diene system as in thebaine (XI).

Pharmacological Testing.—The thebaine–*p*-benzoquinone adduct (II), like thebaine itself, caused convulsions in mice and rabbits, delayed in onset and usually commencing no sooner than ten minutes after intravenous injection. In mice the intravenous LD_{50} was approximately 20 mg./kg. The adduct also exhibited antihistamine properties, concentrations of 10^{-6} g./ml. almost eliminating the effect of histamine (5×10^{-7} g./ml.) on guinea-pig ileum and 3×10^{-7} g./ml. greatly reducing the response.

Pharmacological examination of thebaine–quinol adduct was limited by the low solubility of the base and its salts. Given as a suspension, 200 mg./kg. intraperitoneally produced no overt symptoms in mice. At a concentration of 10^{-5} g./ml. it decreased the motility of isolated ileum and greatly reduced the spasm caused by acetylcholine, histamine, or barium.

The 5′ : 6′-dihydro-compound (V) is a powerful analgesic, its potency being a tenth to a fifth of that of morphine by subcutaneous injection in rats (of the same order as that of pethidine). Its LD_{50} of 150 mg./kg. intravenously in mice is notably different from that of the unreduced compound (II). It showed no significant spasmolytic or antihistamine properties.

The thebaine–but-2-ene-1 : 4-diol " adduct " showed some analgesic effects in rats on subcutaneous injection of 25 mg./kg. The intravenous LD_{50} was about 70 mg./kg., hyperexcitability and Straub tail being observed. In a rabbit it was mildly depressant on intravenous injection, and was slightly mydriatic at 25 mg./kg. intraperitoneally in mice. At a concentration of 10^{-5} g./ml. it reduced the response of guinea-pig ileum to histamine and barium, but not to acetylcholine.

Experimental

Thebaine–p-Benzoquinone (III) (Sandermann;[1] Schöpf, von Gottberg, and Petri[2]).—It was more convenient to carry out this preparation in toluene in open vessels on the water-bath, than under reflux in benzene as previously reported. The product (98%) was obtained as lemon-yellow prisms, m. p. 268° (lit.,[2] 250°).

5′ : 6′-Dihydro-adduct of Thebaine and p-Benzoquinone (V).—The thebaine–*p*-benzoquinone adduct (6 g.) in cold glacial acetic acid (35 ml.) containing platinum oxide (0·1 g.) was shaken under hydrogen at atmospheric pressure until 1 mol. of hydrogen had been absorbed (325 ml. at N.T.P.). The mixture was filtered and diluted with water. On addition of ammonia white crystals were obtained. These were collected, washed with water, and recrystallised three times from 2-ethoxyethanol, the *5′ : 6′-dihydro-adduct* being obtained as colourless elongated plates, m. p. 222° (decomp.), $[\alpha]_D^{20}$ −246° (*c* 1·5 in $CHCl_3$) (Found : C, 71·5, 71·3; H, 6·4, 6·5; N, 3·1, 3·5. $C_{25}H_{27}O_5N$ requires C, 71·2; H, 6·5; N, 3·3%). The m. p. of this compound varied between 204° and 222° in different preparations, and also varied with the rate of heating. Preparations of differing m. p. did not depress each other's m. p., and their identity was confirmed by their infrared absorption spectra. These showed carbonyl absorption at 5·88 and 5·93 μ, proving the saturated ketone structure (IV) [the thebaine–*p*-benzoquinone adduct (II) shows carbonyl bands at 5·96 and 6·06 μ].

The base is very sparingly soluble, except in chloroform and boiling 2-ethoxyethanol; its salts, however, are very soluble in hydrophilic solvents, and even to some extent in chloroform. An *acid hydrochloride* was obtained by the passage of dry hydrogen chloride through a suspension of the base in dry ether. It was recrystallised with difficulty from ethanol–ether (1 : 19), then having m. p. 224—227° (Found : C, 61·0; H, 6·0; Cl, 13·6. $C_{25}H_{27}O_5N,2HCl$ requires C, 60·8; H, 5·9; Cl, 14·5%). The *picrate* was obtained by adding alcoholic picric acid to an alcoholic solution of the hydrochloride, as elongated plates, m. p. 208—212° (from 1 : 1 ethanol–2-ethoxyethanol) (Found : C, 57·2; H, 4·6; N, 8·6. $C_{21}H_{20}O_{12}N_4$ requires C, 57·2; H, 4·6; N, 8·6%).

The *dioxime* was obtained as colourless rhombohedra, m. p. 222°, from ethanol (Found: C, 66·7; H, 6·2; N, 9·2. $C_{25}H_{29}O_5N_3$ requires C, 66·6; H, 6·3; N, 9·3%). The *p*-nitro- and 2 : 4-dinitro-phenylhydrazone were amorphous. No other product of catalytic reduction of the thebaine–*p*-benzoquinone adduct could be isolated.

Tetrahydro-derivative (VI) *of the Thebaine–p-Benzoquinone Adduct.*—The 5′ : 6′-dihydro-compound (V) (5 g.), sodium borohydride (1 g.), and ethanol (50 ml.) were heated together under reflux until all the reactants dissolved, then for a further 90 min., and the mixture allowed to cool slowly to room temperature, whereafter the colourless crystals were collected and recrystallised from ethanol. The *tetrahydro-compound* was thus obtained as needles, m. p. 335° (Found: C, 70·5; H, 6·9. $C_{25}H_{29}O_5N$ requires C, 70·8; H, 6·9%). The infrared spectrum of this base showed a strong OH band at 2·85 μ and a strong band for saturated CO (at 5·88 μ).

Attempted Addition of cyclo*Pentadiene to the Thebaine–p-Benzoquinone Adduct.*—A solution of this adduct (2 g.) and *cyclo*pentadiene (4 g.) in chloroform (15 ml.) was set aside for 7 days. The white crystals that separated were the thebaine–quinol adduct, white needles (from ethanol), m. p. and mixed m. p. 224° (decomp.) (Found: C, 71·4; H, 6·0. Calc. for $C_{25}H_{25}O_5N$: C, 71·6; H, 6·0%).

Thebaine–Diethyl Maleate Adduct (Schöpf, von Gottberg, and Petri [2]).—It was found advantageous to heat the esterification mixture under reflux for 6 hr. instead of keeping it at room temperature for 5 days as recommended.[2] The ester was obtained as colourless prisms, m. p. 150·5° (lit., 151°), from ethanol.

Thebaine–But-2-ene-1 : 4-diol "Adduct" (VII; R = CH_2·OH).—Powdered lithium aluminium hydride (0·86 g.) in dry ether (350 ml.) was heated under reflux for 2 hr. with vigorous stirring (mercury seal) and the ester adduct (20 g.) was extracted from the Soxhlet apparatus directly into the hydride solution. After continuous extraction for 5 hr. all the ester was removed and the mixture was then stirred and heated under reflux for a further hour, then cooled and very cautiously added to 20% aqueous potassium hydroxide (500 ml.). The ether was removed and the aqueous layer extracted with chloroform (3 × 100 ml.). The combined ether and chloroform solutions were dried and evaporated, leaving an oil that crystallised on trituration with moist ether. The *but-2-ene-1 : 4-diol "adduct"* was collected and recrystallised from moist ether as colourless prisms, m. p. 108° (sintering at 98°), $[\alpha]_D^{18}$ −129° (*c* 1 in $CHCl_3$) (Found: C, 65·8, 65·9; H, 7·4, 7·6; N, 3·3, 3·4; H_2O, 4·3, 4·5. $C_{23}H_{29}O_5N,H_2O$ requires C, 66·2; H, 7·4; N, 3·3; H_2O, 4·3%). The *picrate* was prepared in and recrystallised from ethanol, as yellow prisms, m. p. 216—220° (decomp.) (Found: C, 55·4; H, 5·8; N, 8·1; loss at 150°, 5·8. $C_{29}H_{32}O_{12}N_4,C_2H_5$·OH requires C, 55·3; H, 5·7; N, 8·3; C_2H_5·OH, 5·9%).

Attempted catalytic reduction of the base over palladised charcoal afforded elongated plates, m. p. 119—123°, that nevertheless were identified by analysis and by the infrared spectrum as unreduced base monohydrate.

Thebaine–Diethyl Fumarate Adduct.—Thebaine (10 g.) and fumaryl chloride (5 g.) were warmed together in benzene (100 ml.), a deep violet colour developing. Ethyl alcohol was finally added. Colourless prisms separated very slowly and were found to consist of the hydrochloride of a base, presumably the adduct as no colour was observed on dissolving the substance in concentrated hydrochloric acid. The yields were very erratic and the substance could not be obtained analytically pure.

The Thebaine–Naphthaquinol Adduct.—Thebaine (2 g.) and 1 : 4-naphthaquinone (1 g.) were heated in ethanol (20 ml.) for 10 min. on the water-bath. Only a brown amorphous powder was obtained which could not be crystallised from ethanol or methanol (contrast Sandermann [1]). The powder was heated with dilute acetic acid for 5 min., the solution cooled, and the reddish crystals were collected. On recrystallisation from ethanol the *adduct* was obtained as colourless needles, m. p. 224° (decomp.) (Found: C, 74·0; H, 6·0; N, 2·6. $C_{29}H_{27}O_5N$ requires C, 74·2; H, 5·8; N, 2·9%).

Thebaine Methiodide–1 : 4-Naphthaquinone Adduct.—Thebaine methiodide (1 g.) and 1 : 4-naphthaquinone (0·4 g.) were warmed in chloroform (10 ml.). A red colour immediately developed and after 5 min. and rubbing with a glass rod produced pale orange crystals. When washed with aqueous acetone and dried, this *adduct* formed pale orange prisms, m. p. 193° (Found: C, 58·6; H, 4·7; N, 2·5; I, 21·9. $C_{29}H_{27}O_5N$,MeI requires C, 58·9; H, 4·95; N, 2·3; I, 20·9%). Repeated recrystallisation from ethanol gave only thebaine methiodide, m. p. and mixed m. p. 224°.

Attempted Rearrangement of the Thebaine–Maleic Anhydride Adduct.—The adduct (2 g.) was heated with concentrated hydrochloric acid (20 ml.) on the water-bath for 3 hr. On evaporation an acid- and alkali-soluble brown glass was obtained. That this was the thebaine–maleic acid

" adduct " was confirmed by esterification, which gave the diethyl ester, m. p. and mixed m. p. 150°. The same result was obtained when the maleic anhydride adduct was heated with glacial phosphoric acid at 170° for 15 min.

Attempted Addition of 1 : 2-*Naphthaquinone to Thebaine.*—Thebaine (2 g.) and the quinone (1 g.) were heated in nitrobenzene with a few crystals of quinol to prevent polymerisation. The mixture darkened and on removal of the nitrobenzene only a tar was obtained. Reaction in toluene or chloroform gave a red solution from which only thebaine could be recovered, and in ethanol only an amorphous brown solid. This last, when warmed with dilute acetic acid and subsequently neutralised with ammonia, gave an amorphous green precipitate.

Attempted Reaction of β-*Ethylthiocodide with* p-*Benzoquinone.*—β-Ethylthiocodide (m. p. 143°) was heated, in separate experiments, in benzene, toluene, and chloroform with *p*-benzoquinone, to give in each case a red solution from which only tar could be recovered. Reaction with maleic anhydride gave a yellow solution from which only maleic acid was recovered.

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