Tetrahedron. Vol. 25, pp. 3667 to 3673. Pergamon Press 1969. Printed in Great Britain

BIOGENETIC TYPE SYNTHESES OF APORPHINE ALKALOIDS, ISOBOLDINE AND GLAUCINE*

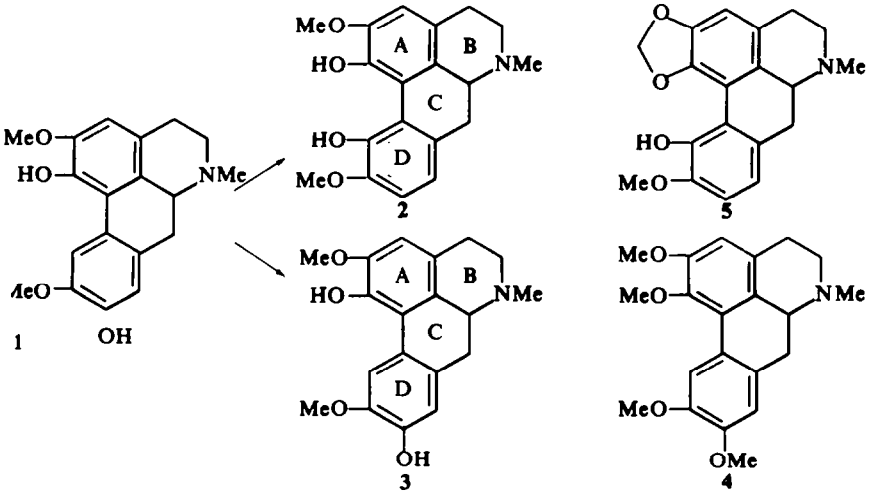
T. KAMETANI†, T. SUGAHARA, H. YAGI and K. FUKUMOTO
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

(*Received in Japan* 10 *February* 1969; *Received in the UK for publication* 17 *March* 1969)

Abstract—Phenolic oxidative coupling of N-ethoxycarbonylnorreticuline (**15**) with potassium ferricyanide gave 6-ethoxycarbonyl-1,9-dihydroxy-2,10-dimethoxyaporphine (**19**), which was also obtained by phenolic oxidative coupling of 1-(2-bromo-5-hydroxy-4-methoxybenzyl)-2-ethoxycarbonyl 1,2,3,4-tetrahydro-7-hydroxy-6-methoxyisoquinoline (**16**), the Br atom being eliminated during the reaction. Reduction of this aporphine (**17**) gave the isoboldine (**3**), which was methylated with diazomethane to afford the glaucine (**4**).

THE aporphine alkaloids are probably biosynthesized oxidatively from the 1-benzyl isoquinolines.[1] Thus, the phenolic oxidative coupling[2] generates the bond between the aporphine rings A and D shown by the transformation of reticuline (**1**) into corytuberine (**2**). Here, corytuberine (**2**) is formed by *ortho-ortho* coupling of reticuline (**1**). On the other hand, *ortho-para* coupling of reticuline (**1**) would give the isoboldine (**3**), which by further methylation could plausibly give rise to the glaucine (**4**).‡ This suggestion was confirmed by the feeding conversion of radio-active reticuline into bulbocapnine (**5**).[3]

CHART 1



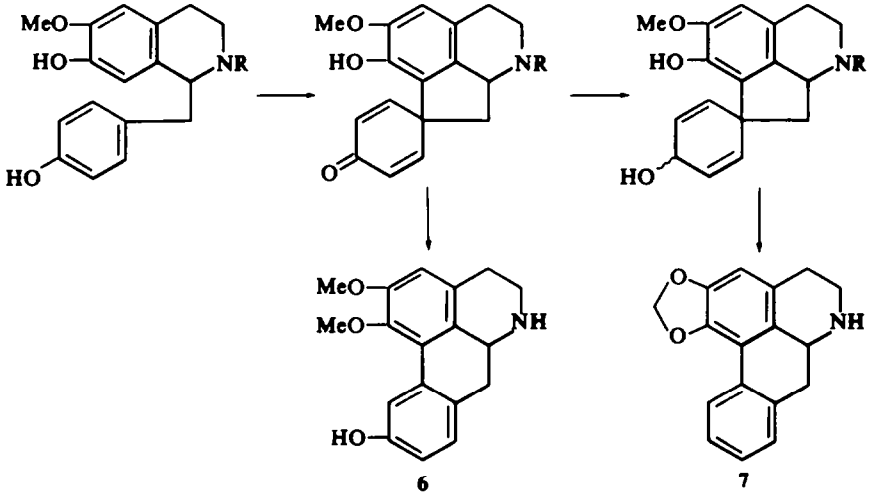
* This paper forms Part CCCXIV by T. Kametani: Part CCCXIII. T. Kametani, H. Iida, T. Kikuchi, K. Ohkubo and K. Fukumoto, *Chem. Pharm. Bull.*, 17, 1051 (1969).

† Correspondence regarding this work should be directed to T. Kametani at this address.

‡ The biogenesis of several aporphine alkaloids, such as tuduranine (**6**) and anonaine (**7**), requires further steps of dienone–phenol or dienol–benzene rearrangement after phenolic oxidative coupling stage.[4]

Another coupling mode which occurs at C-4a in the isoquinoline ring gives morphinandienone type compounds, salutaridine (**8**) and/or isosalutaridine (**9**), the former of which is a key precursor to morphine (**10**).[5] Isosalutaridine (**9**) would biosynthesize the amurine (**11**)[6] and flavinantine (**12**)[7] by subsequent cyclization or transmethylation of *ortho*-methoxyphenol.

CHART 2



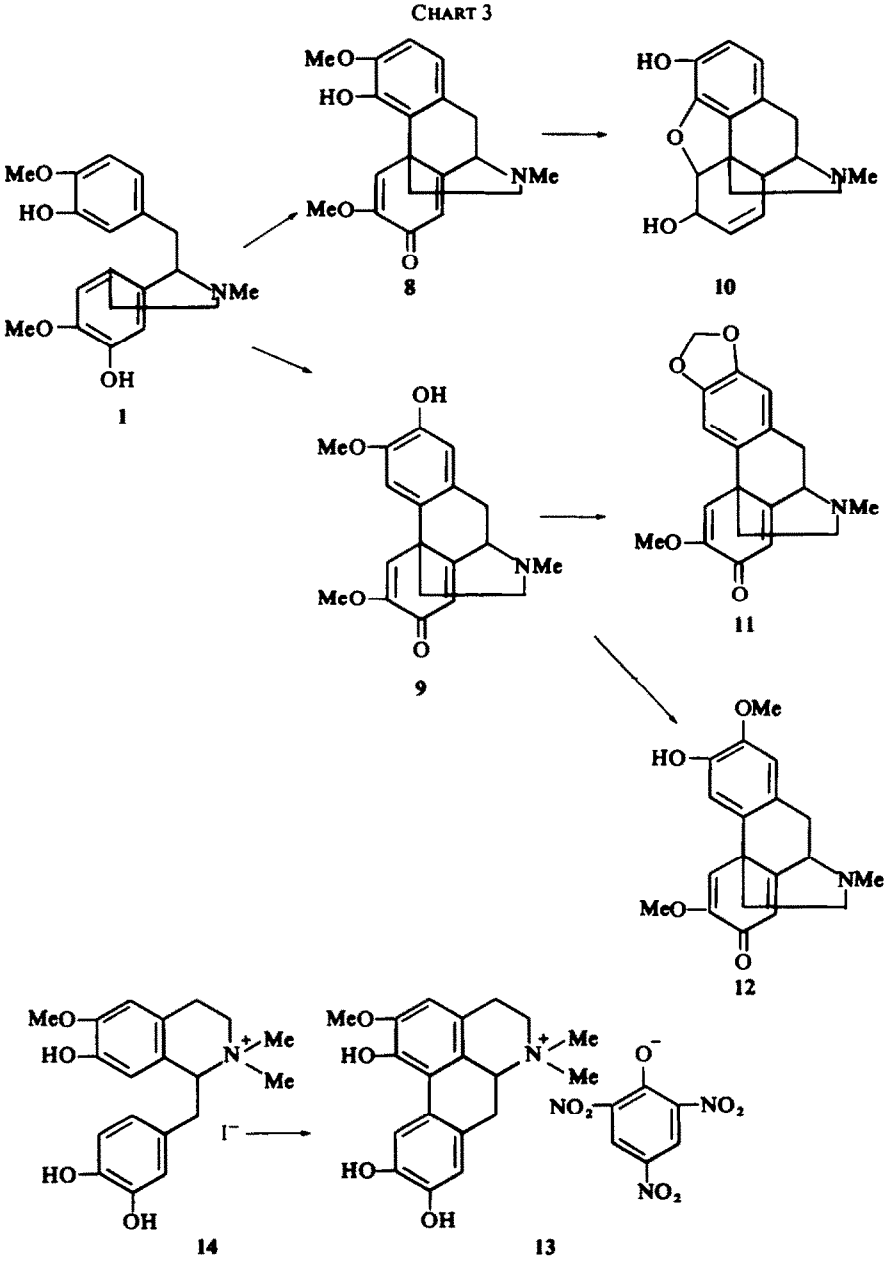
6 **7**

The first stages of both sequences have been achieved in the laboratory by phenolic oxidative coupling of reticuline (**1**) with potassium ferricyanide or manganese dioxide by several groups;[8-12] thus, the present authors[12] oxidized (±)-reticuline (**1**) with potassium ferricyanide in 5% sodium hydrogen carbonate and chloroform solution to give the (±)-isosalutaridine (**8**) and (±)-isoboldine (**3**) in 4·5% and 0·5% yields, respectively. On the other hand, a much higher yield (16·9%) of the salt (**13**) was obtained when the trihydroxyisoquinoline methiodide (**14**) was treated with ferric chloride,[13] partly due to the blocking of nitrogen. In order to examine this possibility, oxidation of the diphenolic N-ethoxycarbonylisoquinolines (**15** and **16**), which would be easily converted into NH and N-Me groups by hydrolysis or reduction in the latter stage, was carried out. These results are now reported.

Norreticuline (**17**)[15] was ethoxycarbonylated with ethyl chlorocarbonate and triethylamine in chloroform and the resulting product (**18**) was hydrolysed partly with alcoholic sodium hydroxide solution to give the starting material, N-ethoxycarbonylnorreticuline (**15**). The oxidative coupling of (**15**) with potassium ferricyanide was examined under a variety of conditions, and the best condition involved a 2-phase system of chloroform and aqueous potassium ferricyanide in ammonia. By this method, the desired aporphine type compound, 6-ethoxycarbonyl-1,9-dihydroxy-2,10-dimethoxyaporphine (**19**), was obtained consistently in 5–7% yield after purification by successive column chromatography on silica gel and alumina.

The structure (**19**) of the above oxidatively coupled product was supported by the spectral data; the UV spectrum having the absorption maxima at 281 and 303 mμ in methanol, which was closely similar to those of glaucine (**4**) (λ_{max}^{EtOH} 281 and 302 mμ),

CHART 3

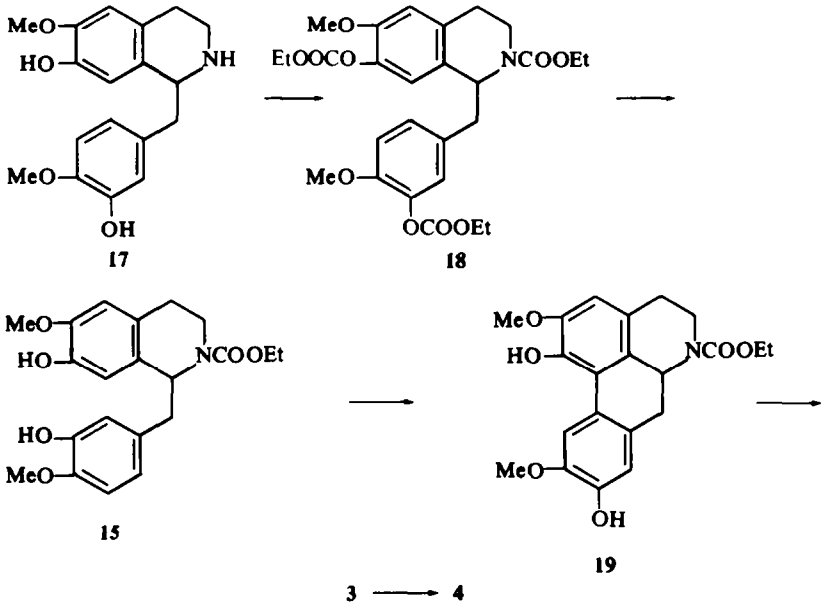


showed this product to be 1,2,9,10-oxygenated aporphine. The NMR spectrum was also consistent with this oxygenation pattern, especially the appearance of a low field resonance at 1·94 τ due to the proton at the C-11 position which was deshielded by both aromatic rings. Moreover, this spectrum also showed the N-ethoxycarbonyl group at 8·71 (triplet, $J = 7$ c/s) and 5·80 τ (quartet, $J = 7$ c/s), O-Me groups at 6·10 τ (6H, overlapped) and aromatic protons at 3·48 (singlet, C-3) and 3·20 τ (singlet, C-

8). The IR spectrum of **19** also revealed the presence of phenolic OH and N-ethoxycarbonyl groups at 3470 and 1673 cm^{-1}, respectively.

N-Ethoxycarbonylaporphine (**19**) was reduced with LAH to give the isoboldine (**3**) in good yield, which showed the absorption maxima at 280 and 305 mμ in methanol (log ε 4·09 and 4·11) in the UV spectrum, and three Me groups at 7·48 (NMe) and 6·14 (6H, two OMe) and three aromatic protons at 3·54 (C-3), 3·28 (C-8) and 2·06 τ (C-11) in its NMR spectrum. These facts are closely similar to those of isoboldine reported earlier,[8] and its IR spectrum is superimposable upon that of the authentic sample.[12] (The (±)-isoboldine (**3**), which was obtained as an unstable pale brown powder, was further converted by methylation with diazomethane into the glaucine (**4**) as a viscous oil (λ_{max}^{MeOH} 281 and 302 mμ), which was characterized as its methiodide, m.p. 216–217°. The UV [λ_{max}^{MeOH} 283 and 303 mμ), (log ε 4·20 and 4·22)] and IR spectra are identical with those of the authentic sample.[13]

CHART 4

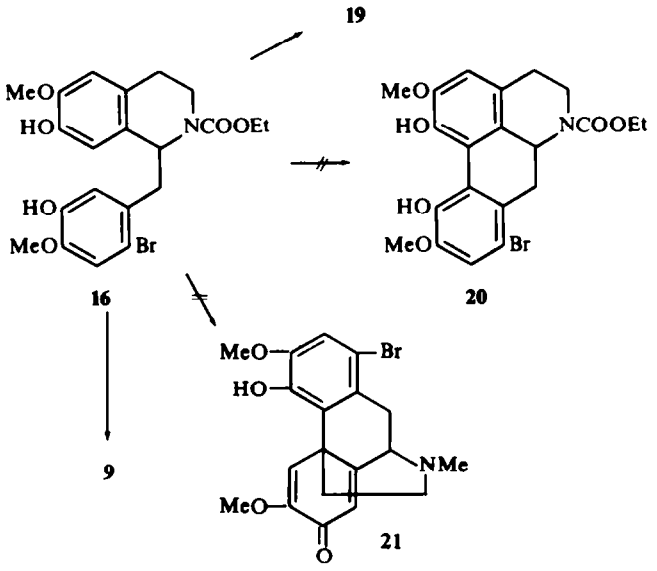


Since we could not detect the formation of 1,2,10,11-oxygenated aporphine in our oxidative coupling reaction, we have investigated the oxidative coupling of the bromoisoquinoline (**16**) in the expectation that the Br atom would inhibit the coupling *para* to the OH group and favour the *ortho*-coupling to give the bromocorytuberine (**20**) type compound. The bromoisoquinoline (**16**) was prepared by the standard method.[14]

The oxidative coupling of the bromoisoquinoline (**16**) with potassium ferricyanide in the same system as used for the N-ethoxycarbonylnorreticuline (**15**) gave 1,2,9,10-oxygenated aporphine (**19**) which eliminated the Br atom during the oxidative coupling reaction. No traces of the desired 1,2,10,11-oxygenated aporphine (**20**) or dienones (**9** and **21**), could be detected either spectroscopically or by TLC. This

abnormal, rather surprising, reaction is known,[8] and the mode of elimination of the Br atom in this oxidation is not readily apparent. Assuming that the radical pairing mechanism is involved, the most likely fate of the Br is elimination as a bromonium ion to give hypobromous acid, and the radical or anionic substitution mechanisms seem much less favourable.[8]

CHART 5



The inability of our compounds (**15** and **16**) to form 1,2,10,11-oxygenated aporphine is due probably to the influence of steric factor which prevents direct coupling of radicals at *ortho* position to the two phenolic OH groups concerned. This suggestion is partially supported by the UV,[16] ORD[16] and NMR spectral data,[17] which show that the substituents at the C-1 and C-11 positions in aporphines cause to some extent twisting of the biphenyl ring system from coplanarity.

The above results do not support the suggestion that the blocking of the nitrogen is essential for the aporphine syntheses from 1-benzylisoquinolines, and also seem to indicate the formation of 1,2,10,11-oxygenated aporphines by direct oxidative coupling reaction to be difficult in the laboratory.

EXPERIMENTAL

M.ps are uncorrected. The IR spectra were taken in $CHCl_3$ soln unless otherwise noted with a Hitachi EPI-S_2 spectrophotometer. UV spectra were taken in MeOH soln on a Hitachi EPS-3 recording spectrophotometer. NMR spectra were measured on a Hitachi H-60 in $CDCl_3$ soln using TMS as an internal standard.

2-Ethoxycarbonyl-1,2,3,4-tetrahydro-7-hydroxy-1-(3-hydroxy-4-methoxybenzyl)-6-methoxyisoquinoline (*N-ethoxycarbonylnorreticuline*) (**15**). To a soln of 7 g of **17**[15] and 8 g of Et_3N in 100 ml $CHCl_3$, 8 g ethyl chloroformate was added dropwise with stirring for 30 min at 10°. The reaction mixture was allowed to stand at room temp for 30 min, washed with water and dried over K_2CO_3. Evaporation of the solvent gave 7·7 g of **18** as a pale reddish syrup, the IR spectrum exhibits absorptions at 1758 (OCOOEt) and 1675 cm^{-1} (NCOOEt). A mixture of 7·7 g of the above syrup, 40 ml EtOH, 2 g NaOH, and 3 ml water was refluxed for 15 min. After evaporation of the solvent, a mixture of the resultant residue and 100 ml water was saturated with the excess crystalline NH_4Cl and extracted with $CHCl_3$. The extract was

washed with water, dried over Na_2SO_4, and evaporated to give 6 g of a pale brown syrup, the IR spectrum shows absorptions at 3500 (OH) and 1675 cm^{-1} (NCOOEt). The NMR spectrum shows a triplet at τ 8·88 ($NCOOCH_2\underline{CH_3}$, J = 7 c/s), a singlet at 6·22 (2 × OCH_3), a quartet at τ 4·95 ($NCOOC\underline{H_2}CH_3$, J = 7 c/s, and broad signal at τ 4·95 (2 × OH, disappeared with the addition of D_2O).

Phenol Oxidation of **15**. To a soln of 900 mg potassium ferricyanide in 400 ml 16% NH_4OH, a soln of 512 mg of **15** in 200 ml $CHCl_3$ was added dropwise with vigorous stirring at room temp for 30 min in a current of N_2. The stirring was continued for further 30 min, and the $CHCl_3$ layer was separated, washed with water and dried over Na_2SO_4. Evaporation of the solvent gave 500 mg of a dark reddish syrup, which was chromatographed on 10 g silica gel using $CHCl_3$ containing 1% MeOH as the eluent for inspection by its IR spectrum. Evaporation of the appropriate fraction gave 40 mg of a pale reddish gum which was further purified by chromatography on 3 g alumina to give 32 mg **19** as a yellowish gum. The UV spectrum (MeOH) shows absorption maxima at 281 mμ and 303 mμ; the IR spectrum ($CHCl_3$) exhibits absorption at 3470 cm^{-1} (OH), and 1673 cm^{-1} (NCOOEt). The NMR spectrum shows a triplet at τ 8·71 ($NCOOCH_2\underline{CH_3}$, J = 7 c/s), a singlet at τ 6·10 (2 × —OCH_3), a quartet at τ 5·80 (—$NCOOC\underline{H_2}CH_3$, J = 7 c/s), and three aromatic protons at τ3·48 (C_3—H), 3·20 (C_8—H) and 1·94 (C_{11}—H).

(±)-*Isoboldine* (**3**) (1,9-*dihydroxy*-2,10-*dimethoxy*-2-*methylaporphine*). A mixture of 70 mg of **19**, 100 mg LAH, and 80 ml dry THF was refluxed on a water-bath for 10 hr. After addition of 1 g crystalline NH_4Cl, the inorganic ppt was removed by filtration. Evaporation of the filtrate gave a dark reddish gum which was extracted with $CHCl_3$, washed with water, and dried over Na_2SO_4. Evaporation of the solvent gave 40 mg of a dark reddish gum which was purified by silica gel chromatography using $CHCl_3$ containing 1% MeOH as an eluent to give 25 mg of (±)-isoboldine as a pale brown powder, which darkened rapidly on attempted recrystallization. The IR ($CHCl_3$) spectrum was superimposable with that of the authentic sample.[12] The UV spectrum (MeOH) shows the absorption maxima at 280 mμ (log ε: 4·09) and 305 mμ (log ε: 4·11); the NMR spectrum shows the three Me groups at τ 7·48 (—$NC\underline{H_3}$) and 6·14 (2 × $OC\underline{H_3}$), and three aromatic protons at 3·54 (C_3—H) 3·28 (C_8—H) and 2·06 (C_{11}—H).

(±)-*Glaucine* (**4**) *methiodide*. A soln of 25 mg of **3** in 10 ml MeOH was kept overnight with excess diazomethane in ether. Removal of the excess diazomethane and solvent gave 26 mg of a yellowish gum, the UV spectrum (MeOH) shows absorption maxima at 281 mμ and 302 mμ. Recrystallization of the methiodide from MeOH–ether gave colourless prisms, m.p. 216–217°. The UV spectrum [λ_{max} 283 mμ and 303 mμ (log ε 4·20 and 4·22) (in MeOH)] and the IR spectrum (KBr) are superimposable with those of the authentic sample.[13]

1-(2-*Bromo*-5-*hydroxy*-4-*methoxybenzyl*-2-*ethoxycarbonyl*-1,2,3,4-*tetrahydro*-7-*hydroxy*-6-*methoxyisoquinoline* (**16**). To a soln of 3 g 6′-bromonorreticuline[14] and 3·1 g Et_3N in 350 ml $CHCl_3$, 2·6 g of ethyl chloroformate was added dropwise with stirring for 30 min under cooling with ice. The reaction mixture was allowed to stand at room temp for 30 min, washed with water and dried over Na_2SO_4. Evaporation of the solvent gave 3·3 g of a brownish syrup [the IR spectrum exhibited absorptions at 1760 cm^{-1} (—OCOOEt) and 1680 cm^{-1} (—NCOOEt)]. A soln in a mixture of 15 ml EtOH, 1 g NaOH and 1 ml water was refluxed for 15 min. After evaporation of the solvent, a mixture of the resultant residue and 80 ml water was saturated with the excess crystalline NH_4Cl and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 3 g colourless prisms, m.p. 215–217°. (Found: C, 53·62; H, 5·30; N, 3·36. $C_{21}H_{24}NO_6Br$ requires: C, 53·87; H, 5·19; N, 3·00%).

Phenol oxidation of **16**. To a soln of 9 g potassium ferricyanide in 600 ml 16% NH_4OH, a soln of 3 g of **16** in 600 ml $CHCl_3$ was added dropwise with vigorous stirring at room temp for 40 min in a current of N_2. The stirring was continued for further 40 min, and the $CHCl_3$ layer was separated, washed with water and dried over Na_2SO_4. Evaporation of the solvent gave 2·3 g of a dark reddish syrup, which was treated as in case of phenol oxidation of **15** to afford 70 mg of **19**. The IR and NMR spectra are superimposable with the authentic sample obtained by phenol oxidation of **15** described above.

Acknowledgements—The authors wish to thank Miss R. Hasebe and Miss A. Kawakami for microanalyses, and Miss Y. Tadano for the NMR determinations.

REFERENCES

[1] R. Robinson, *The Structural Relations of Natural Products* Clarendon Press, Oxford (1955) and refs cited therein.

[2] D. H. R. Barton and T. Cohen, *Festschrift Arthur Stoll* p. 114. Birkhauser, Basel (1957).

[3] G. Blaschke, *Arch. Pharm.* **301**, 432 (1968).

[4] A. R. Battersby, *Proc. Chem. Soc.* 189 (1963).

[5] D. H. R. Barton, G. W. Kirby, W. Steglich, G. M. Thomas, A. R. Battersby, T. A. Dobson and H. Ramuz, *J. Chem. Soc.* 2423 (1965) and refs cited therein.

[6] W. Döpke, H. Flentje and P. W. Jeffs, *Tetrahedron* **24**, 4459 (1968).

[7] C. Chamber and K. L. Stuart, *Chem. Comm.* 328 (1968).

[8] A. H. Jackson and J. A. Martin, *Ibid.* 420 (1965); *J. Chem. Soc.* (C) 2061 (1966).

[9] W. W.-C. Chan and P. Maitland, *Ibid.* (C) 753 (1966).

[10] D. H. R. Barton, D. S. Bhakuni, R. James and G. W. Kirby, *Ibid.* (C) 128 (1967).

[11] B. Franck, G. Dunkelmann and H. J. Lubs, *Angew. Chem.* **79**, 1066 (1967).

[12] T. Kametani, K. Fukumoto, A. Kozuka and H. Yagi, *J. Chem. Soc.* (C), in press.

[13] T. Kametani and I. Noguchi, *J. Chem. Soc.* (C) 1440 (1967); cf. B. Franck and G. Blaschke, *Liebigs Ann.* **659**, 123 (1962).

[14] T. Kametani and M. Ihara, *J. Chem. Soc.* (C), 230 (1967).

[15] M. Tomita and J. Kunitomo, *J. Pharm. Soc. Japan* **80**, 1238 (1960).

[16] C. Djerassi, K. Mislow and M. Shamma, *Experientia* **18**, 53 (1962); M. Shamma, *Ibid.* **16**, 484 (1960).

[17] S. Goodwin, J. Shoolery and L. F. Johnson, *Proc. Chem. Soc.* 306 (1958); R. C. Bick, J. Harley-Mason, N. Sheppard and M. Vernengo, *J. Chem. Soc.* 1896 (1961); W. H. Baarshers, R. R. Arndt, K. Pachler, J. A. Weisbach and B. Douglas, *Ibid.* 4778 (1964).