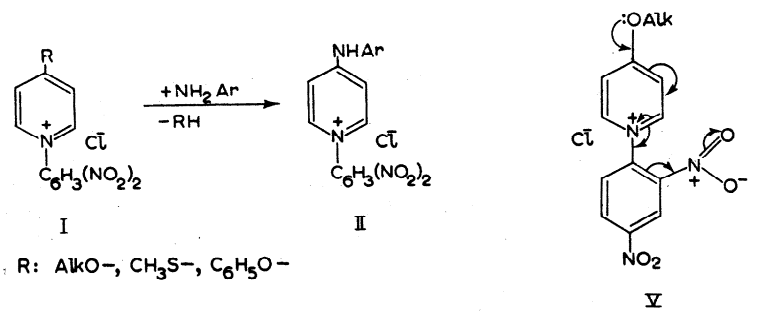
Tetrahedron, 1958, Vol. 2, pp. 361–366. Pergamon Press Ltd., London

PRELIMINARY COMMUNICATIONS

New conversions of pyridinium salts and syntheses of γ-amino-substituted pyridines*

(*Received* 31 *July* 1957)

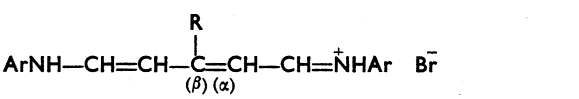
IN an earlier paper an attempt to effect the pyridine ring cleavage in γ-alkoxy-, phenoxy- and methylmercapto-substituted pyridines by treating N-2, 4-dinitrophenylpyridinium chlorides(I) with aromatic amines was described.[1] The results showed that the pyridine ring does not open, the arylamino group being substituted for γ-alkoxy(methylmercapto-, phenoxy) group, to form N-2,4-dinitrophenyl-γ-arylamino pyridinium chlorides (II), as follows:



I II V

R: AlkO–, CH_3S–, C_6H_5O–

Later the cleavage of the pyridine ring in γ-alkoxy (methylmercapto-, phenoxy)pyridines was effected by treating these compounds with cyan bromide and aromatic amines.[2] β-Alkoxy(methylmercapto-, phenoxy) substituted glutaconaldehyde anil anilide hydrobromide (III) were obtained.



III

R:AlkO—, CH_3S—, C_6H_5O—.

Of these compounds the β-alkoxy have been shown to be highly unstable even in crystalline state.† Particularly unstable are their alcoholic solutions, which quickly decolorise when heated. The preparations on being stored, especially in summer time, gradually turn into yellowish crystalline line substances impregnated with liquid. The β-phenoxyglutaconaldehyde anil anilide hydrobromide is somewhat more stable. Yet it also decomposes on heating or when stored for a long time.

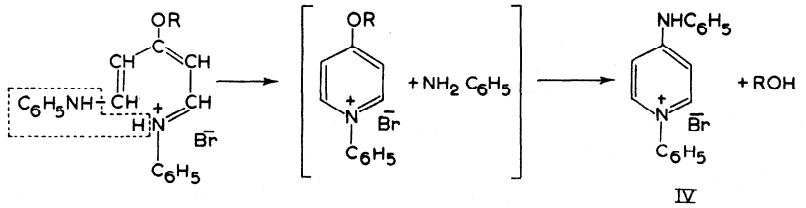
Investigation of the crystalline products obtained from the conversion of anil anilide salts (III; Ar = C_6H_5-, R = —OAlk, —OC_6H_5) showed them to be the same compound, namely N-phenyl-γ-phenylamino pyridinium bromide (IV), obtained as pale yellow hygroscopic needles, m.p. 192–193°.

* Translated by A. L. Pumpiansky, Moscow.

† This seems to have been the reason why Ebert did not succeed in effecting the cleavage of γ-methoxypyridine with cyan bromide and aniline. He failed to isolate β-methoxyglutaconaldehyde anil anilide hydrobromide.[3]

[1] A. F. Vompe, N. F. Turitsyna and I. I. Levkojev *Dokl. Akad. Nauk SSSR* **65**, 839 (1949).
[2] A. F. Vompe *On the cleavage of pyridine bases* D.Sc. Thesis, Moscow (1951).
[3] G. Ebert Dissertation, Dresden (1913).

(Found (after drying *in vacuo* at 40–50°): N, 8·52, 8·39; Br, 24·45, 24·68. Calc. for $C_{17}H_{15}N_2Br$: N, 8·57; Br, 24·44%). The formation of compound (IV) proceeds according to the general scheme:



IV

R: CH_3– ..... iso C_5H_{11}–, C_6H_5– etc.

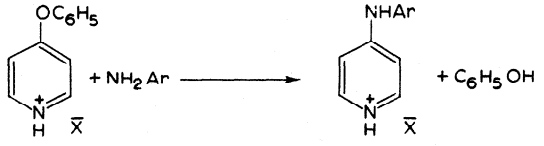
The products of decomposition of the β-phenoxyderivative (III) were found to contain phenol. Thus, the cyclisation reaction of glutaconaldehyde anil anilide salts into N-arylpyridinium salts, due to Zincke, which usually requires rigid conditions (melting, heating with concentrated hydrochloric acid, etc.),[4] proceeds very readily in this particular case.

Conversions studied can be considered as part of the general substitution reaction of γ-alkoxy-(phenoxy) groups by the aromatic amine substituents in pyridinium salts containing electronegative radicals ($C_6H_3(NO_2)_2$-, C_6H_5-) at the cyclic nitrogen (cf. ref. 1). Undoubtedly one is dealing with the conjugation of *p*-electrons of the oxygen atom in the —OAlk(—OC_6H_5) group with the other part of the pyridinium salt molecule (see e.g. V) that imparts to these molecules the oxonium salt properties. (cf. ref. 5).

β-Methylmercaptoglutaconaldehyde anil anilide hydrobromide (III; Ar = C_6H_5-, R = —SCH_3) readily undergoes cyclisation, the reaction, however, ceasing at the stage of N-phenyl-γ-methyl-mercaptopyridinium bromide formation. Such a reaction is easy to understand if one bears in mind that the sulphur atom in N-phenyl-γ-methylmercaptopyridinium bromide is partly in the onium state (anologically V) sulphonium salts being less reactive than those of oxonium.

The increase of the electronegativity of the radical linked with the nitrogen atom in γ-methyl-mercaptopyridine (due to the dinitrophenyl radical being substituted for the phenyl one) results in the amine substituent being substituted for the methylmercapto group, N-2,4-dinitrophenyl-γ-methylmercaptopyridinium chloride reacting with aromatic amines, though somewhat slower than γ-alkoxyderivatives (cf. 1).

The problem of the lability of the alkoxy group in N-alkyl-γ-alkoxypyridinium halide was next investigated. The reaction of γ-methoxypyridine methiodide with aniline (in alcoholic solution when heated on a water-bath) results in the removal of methyl iodide and formation of N-methyl-γ-pyridone, no γ-phenylaminopyridine methiodide being found. It follows that to render the alkoxy group capable of being substituted it is not sufficient to make the cyclic nitrogen atom assume the tetravalent state but this atom must in addition be linked to an electronegative radical.



VI

Ar: C_6H_5–(94–96), (p) $CH_3C_6H_4$–(86), (o) $CH_3C_6H_4$–(~58), (p) ClC_6H_4–(~73), (p) $CH_3OC_6H_4$–(83), α–$C_{10}H_7$–(42) */

* The percentage yields of γ-arylaminopyridines (VI) are indicated in brackets.

The possibility of substituting the phenoxy group in γ-phenoxypyridine methiodide by aromatic amine substituents was investigated. The splitting off of the aryl halide (under the action of aromatic amine) seemed in this case to be unlikely. Heating γ-phenoxypyridine methiodide with aniline at 115–120° yielded γ-phenylaminopyridine methiodide in 88 per cent yield.

[4] Th. Zincke, G. Heuser and W. Möller *Liebigs Ann.* **333**, 328 (1904).

[5] H. Meerwein, G. Hinz, P. Hofman, E. Kroning and E. Pfeil *J. Prakt. Chem.* **147**, No. 2, 257 (1937); H. Meerwein, E. Battenberg, H. Gold, E. Pfeil and G. Willfang *J. Prakt. Chem.* **154**, No. 2, 83 (1939)

It has also been found that the exchange of the arylamino group for the phenoxy group takes place readily when heating the mixture of γ-phenoxypyridine hydrohalide and the aromatic amine or the salt of the amine and γ-phenoxypyridine. No exchange of the phenoxy group takes place when heating the mixture of the salts of γ-phenoxypyridine and aromatic amines. It has thus been shown that both γ-phenoxypyridinium cation and the free amine participate in the reaction. This naturally suggested carrying out the reaction of γ-phenoxypyridine with the salts of aliphatic amines as well as with ammonium salts, e.g. ammonium chloride. It has been found that the phenoxy group can in this way be substituted by the amino group or substituents of primary and secondary aliphatic amines. Thus, on fusing γ-phenoxypyridine and *cyclo*hexylamine hydrobromide at 200–210° for 1 hr, γ-*cyclo*hexylaminopyridine was obtained in 72 per cent yield (colourless prisms from ether), m.p. 147–148°. Found: N, 15·87, 16·05. Calc. for $C_{11}H_{16}N_2$: N, 15·90%). Similarly γ-dimethylaminopyridine was synthesised by heating γ-phenoxypyridine with dimethylamine hydrobromide for 1 hr at 190–200°. Yield 82 per cent (colourless plates m.p. 112–113°; picrate m.p. 204–206°. (cf. ref. 6)

It has also been found that heating γ-phenoxypyridine with ammonium chloride in an open vessel at 300–310° for 1 hr gives γ-aminopyridine yield 90–95 per cent. To extract γ-aminopyridine from the aqueous solution, use was made of *n*-butanol, which simplifies the isolation of the base.

The preparation of γ-aminopyridine by this method is simpler and more convenient than the syntheses of Koenigs and Greiner[7] and Hertog and Overhoff.[8] These, cannot be used to synthesise γ-aminopyridines substituted on the amino group, whilst the reaction now investigated can be successfully applied as a general procedure for obtaining various γ-aminosubstituted pyridines.

It is to be noted that γ-phenoxypyridine reacting with amine salts behaves similarly to 9-phenoxyacridine.[9] This analogy could, however, hardly be foreseen as 9-alkoxyacridines are known to react with amine salts differently from γ-alkoxysubstituted pyridines and quinolines.[10]

At the conclusion of this investigation a paper by Jerchel *et al.*[11] appeared dealing with the reaction of γ-pyridyl-pyridynium salts, in which the possibility of synthesising γ-aminopyridine from the reaction of γ-phenoxypyridine and ammonia was indicated. No experimental details were given.

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[6] E. Koenigs, H. Friedrich and H. Jurany *Ber. Dtsch. Chem. Ges.* **58**, 2275 (1925).
[7] E. Koenigs and H. Greiner *Ber. Dtsch. Chem. Ges.* **64**, 1054 (1931).
[8] H. J. den Hertog and J. Overhoff *Rec. Trav. Chim.* **69**, 468–473 (1950); cf. E. Ochiai *J. Org. Chem.* **18**, 534 (1953).
[9] N. S. Drosdov and O. M. Tcherntsov *Zh. Obsch. Khim.* **5**, 1736 (1935).
[10] H. J. Barber, J. H. Wilkinson and W. G. H. Edwards *J. Soc. Chem. Industr.* **66**, 411 (1947).
[11] D. Jerchel, H. Fischer and K. Thomas *Chem. Ber.* **89**, 2921 (1956).

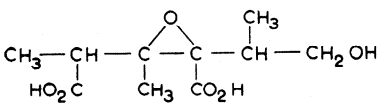
The structures of jaconecic and *iso*jaconecic acids

(*Received* 17 *September* 1957)

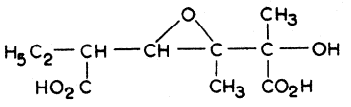
JACONECIC acid ($C_{10}H_{16}O_6$) to which we have tentatively assigned structure (I),[1,2] has been more recently obtained from the alkaloid tomentosine ($C_{19}H_{27}O_7N$) by Adams, Gianturco and van Duuren[3] who propose, without additional evidence structure (II).

*iso*Jaconecic acid ($C_{10}H_{16}O_6$), which together with jaconecic acid is obtained from jacobine, jaconine and the chlorodilactone ($C_{10}H_{13}O_4Cl$), would also be an expected product from the alkaline

[1] R. B. Bradbury *Chem & Ind. (Rev.)* 1021 (1954).
[2] R. B. Bradbury and J. B. Willis *Aust. J. Chem.* **9**, 258 (1956).
[3] R. Adams, M. Gianturco and B. L. van Duuren *J. Amer. Chem. Soc.* **78**, 3513 (1956).



I



II

hydrolysis of tomentosine[3] and othosenine,[4] but was apparently overlooked by the American[5] and Russian[4] workers.

This report concerns the reactions of jaconecic and *iso*jaconecic acids with ferric chloride, acetic anhydride and lead tetra-acetate, which were, amongst other results previously regarded[3] as conflicting with formula (I). Pure jaconecic and *iso*jaconecic acids give negative and positive reactions respectively with ferric chloride, and previously obtained faint positive reactions with jaconecic acid must have been due to contamination with *iso*jaconecic acid. That *iso*jaconecic acid is an α-hydroxy acid and the oxygen atom α- to the carboxyl group in jaconecic acid is part of an oxygen containing ring is confirmed by periodic acid oxidation of the lithium aluminium hydride reduction products ($C_{10}H_{20}O_4$) of dimethyljaconecate and dimethyl*iso*jaconecate which consume 0·2 and 1·3–1·8 mol. per mol. substance respectively, and the reduction product from dimethyl*iso*jaconecate yields formaldehyde. Jaconecic acid with acetic anhydride gives an acetate anhydride ($C_{12}H_{16}O_6$) which indicates, should Blanc's rule be valid, that it contains three or fewer carbon atoms between the carboxyl groups, and cannot be represented by formula (II). This is further confirmed by the reaction of jaconecic acid with lead tetra-acetate at 100°, which yields carbon dioxide, acetaldehyde, (+) β-methyllaevulinic acid (III) and (+) β-methyl-γ-carboxy-γ-valerolactone (IV), derivatives of the last two products being compared with synthetic specimens.

However *iso*jaconecic acid under the same conditions yields a keto-acid $C_9H_{14}O_4$ (V), which although it forms a normal semicarbazone breaks down with 2 : 4-dinitrophenylhydrazine in 2 N hydrochloric acid to a derivative of methylacetoacetic acid. However attempts to prepare an authentic specimen of this derivative results in the formation of the pyrazolone.

It has previously been shown[6] that nitric acid oxidation of jaconecic acid yields α, β-dimethylmalic acid and two other dibasic acids $C_9H_{14}O_6$ and $C_9H_{12}O_7$, whilst *iso*jaconecic acid is but slightly attacked under the same conditions.[7]

To formulate jaconecic and *iso*jaconecic acids it is logical to attempt to add three carbon and one oxygen atoms to the largest identified fragment: β-methyl-γ-carboxy-γ-valerolactone (IV), so that three carbon methyl groups result, and the oxygen atom can (1) form a second five membered ring with the γ-carboxyl group, (2) explain acetaldehyde formation and (3) be etherified in *iso*jaconecic acid and acetylated in jaconecic acid. The α- and β-positions are eliminated on the grounds that only one potential α-hydroxy acid group is present and that acetaldehyde formation is not explained. The only other alternative, the γ-position implies that the methyl group already present migrates from some other part of the molecule, and the formation of methylacetoacetic acid and α, β-dimethylmalic acid suggests the α-position as the source. This fixes the ring structure of the chlorodilactone (VI) in which the two rings are joined by one, rather than two carbon atoms as in formula (VII) proposed by Adams *et al.*[3] and the resemblance of (VI) to monocrotalic acid (X) which yields dimethylmaleic anhydride with nitric acid[8] is added confirmation. The structures now proposed for jaconecic acid (VIII), *iso*jaconecic acid (IX) and the chlorodilactone (VI), which were foreshadowed in our first paper[1] differ from those recently suggested[2] by the placement of a methyl group, which makes the hydroxyl group in (VIII) secondary rather than primary. No structure has yet been proposed by Adams for *iso*jaconecic acid and that given for jaconecic acid (II) and the chlorodilactone (VII) cannot be reconciled with our experimental results. The resistance of the tetrasubstituted glycidic acid grouping in jaconecic acid towards acid hydrolysis is paralleled by similar non-reactivity of the trisubstituted group in β-bromopicrotoxininic acid.[9]

Adams *et al.* have attributed the increased reactivity of jacobine compared with jaconecic acid towards hydrochloric acid, to the catalytic effect of the liberated base, but experiment has shown[7]

[4] E. S. Zhdanovich and G. P. Men'shikov *J. Gen. Chem., Moscow* **11**, 835 (1941).
[5] R. Adams and M. Gianturco *Angew. Chem.* **69**, 5 (1957).
[6] R. B. Bradbury *Aust. J. Chem.* **9**, 521 (1956).
[7] R. B. Bradbury Unpublished results.
[8] R. Adams and J. M. Wilkinson *J. Amer. Chem. Soc.* **65**, 2203 (1943).
[9] H. Conroy *J. Amer. Soc.* **79**, 1726 (1957).

that the chlorodilactone (VI) is not formed from jaconecic acid even in the presence of retronecine hydrochloride. A more plausible explanation would seem to be that conversion of jacobine, jaconine and the chlorodilactone to jaconecic acid involves inversion of configuration at the chlorine containing carbon atom,[10] and that this new configuration is less susceptible to carbonium ion formation (S_N1 mechanism[11]), or more likely to nucleophilic attack by chloride ion (S_N2 mechanism). The free carboxyl group by the formation of an internal salt (XI) might also render the epoxide group less accessible to attack. It is hoped to publish a full account of this work elsewhere.

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[10] S. Winstein and R. B. Henderson *Heterocyclic Compounds* (Edited by Elderfield) Vol. I, p. 11. Wiley, New York (1950); S. Winstein and H. J. Lucas *J. Amer. Chem. Soc.* **61**, 1576 (1939).
[11] F. A. Long, J. G. Pritchard and F. E. Stafford *J Amer. Chem. Soc.* **79**, 2362 (1957), and earlier papers.

11-Alkylated steroids—I. The synthesis of 11-methylhydrocortisone acetate

(*Received* 7 *October* 1957)

THE unreactivity of an 11-ketone function in steroids to the usual carbonyl reagents is well known.[1,2] With the exception of a recent example of the formation of a steroid 11-cyclic acetal[3] only chemical or catalytic reduction to the 11-hydroxyl function[2,4] or to an 11-desoxy steroid[2,5] have been reported.

We wish to report the synthesis of 11-methylhydrocortisone acetate, illustrating the addition of an organometallic reagent to a steroid 11-ketone.

Treatment of 21-hydroxypregna-4,17(20)-[*cis*]-diene-3,11-dione acetate[6] with ethylene glycol and *p*-toluenesulfonic acid in refluxing benzene gave 21-hydroxypregna-5,17(20)-[*cis*]-diene-3,11-dione 3-ethylene acetal acetate (Ia), m.p. 160–162°.

Anal. Calcd. for $C_{25}H_{34}O_5$: C, 72·43; H, 8·27. Found: C, 72·11; H, 8·44. The compound was hydrolyzed with aqueous methanolic potassium bicarbonate to the free alcohol (Ib), m.p. 113·5–115°.

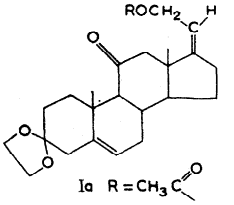
Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74·16; H, 8·66. Found: C, 74·05; H, 8·95. Reaction of Ib with triphenylmethyl chloride in dry pyridine at room temperature gave the 21-trityl ether (Ic), m.p. 201–203°.

Anal. Calcd. for $C_{42}H_{46}O_4$: C, 82·05; H, 7·54. Found: C, 81·99; H, 7·47. The latter was smoothly converted with a sixfold excess of methyllithium in benzene–ether at room temperature to 11β-hydroxy-11-methyl-21-triphenylmethoxypregna-5,17(20)-[*cis*]-dien-3-one ethylene acetal (II), m.p. 182–184°.

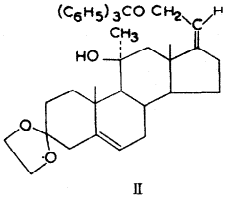
Anal. Calcd. for $C_{43}H_{50}O_4$: C, 81·87; H, 7·99. Found: C, 81·90; H, 7·95; γ_{max}^{Nujol} (cm^{-1}): 3480 (OH); 1672 (Δ^5); 1094, 1002 (C—O); 1596, 1492, 714, 698 (C_6H_5). (When methylmagnesium iodide was substituted for methyllithium only unchanged Ic was recovered. Attempted addition of

[1] D. H. R. Barton *Synthesis and Metabolism of Adrenocortical Steroids. Ciba Foundation Colloquia on Endocrinology* (Edited by W. Klyne) Vol. VII, p. 37. Little, Brown, Boston (1953).
[2] L. F. Fieser and M. Fieser *Natural Products Related to Phenanthrene* (3rd Ed.) pp. 409–410. Reinhold Publishing, New York (1949).
[3] B. J. Magerlein and R. H. Levin *J. Amer. Chem. Soc.* **77**, 1904 (1955).
[4] L. H. Sarett, M. Feurer and K. Folkers *Ibid.* **73**, 1777 (1951); N. L. Wendler, Huang-Minlon and M. Tishler *Ibid.* **73**, 3818 (1951); H. Heyman and L. F. Fieser *Ibid.* **73**, 5252 (1951); H. L. Herzog, M. A. Jevnik and E. B. Hershberg *Ibid.* **75**, 269 (1953); F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi *Ibid.* **75**, 1282 (1953).
[5] R. B. Moffett and J. H. Hunter *Ibid.* **73**, 1973 (1951).
[6] J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze and R. W. Jackson *Ibid.* **77**, 4436 (1955).

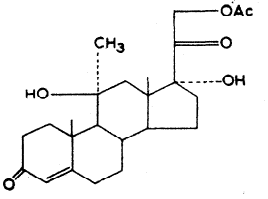
either the Grignard reagent or methyllithium to Ia or Ib gave only Ib.) Hydrolysis of II with dilute methanolic hydrochloric acid at room temperature removed both the trityl and ketol groups, giving 11β,21-dihydroxy-11-methylpregna-4,17(20)-[*cis*]-dien-3-one (IIIa), m.p. 188–192°.



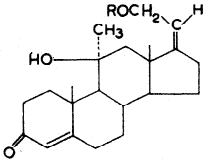
Ia R = $CH_3C(=O)$–
Ib R = H–
Ic R = $(C_6H_5)_3C$–



II



IV



IIIa R = H–
IIIb R = $CH_3C(=O)$–

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76·70; H, 9·36. Found: C, 76·35; H, 9·33. Treatment of IIIa with acetic anhydride pyridine at 25°C gave the corresponding 21-acetate IIIb, m.p. 109–112°.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74·57; H, 8·87. Found: C, 74·66; H, 8·97. When IIIb was treated with N-methylmorpholine oxide peroxide in *t*-butyl alcohol–pyridine containing a catalytic amount of osmium tetroxide,[7] there was obtained, in addition to unchanged IVb and more polar material, 11-methylhydrocortisone acetate (V), m.p. 191–195°.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68·87; H, 8·19. Found: C, 68·85; H, 8·22. γ_{max}^{Nujol} (cm^{-1}): 3400, 3345 (OH); 1744, 1724 (C=O); 1631 (conj. C=O), 1606 (Δ^4), 1232 (C—O acetate) λ_{max}^{EtOH} 243 mμ, a_M 16,350. This material reduced Tollens' reagent.

We have assigned the introduced 11-methyl group* the α-configuration largely on the basis of stereochemical considerations.

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* Unpublished studies by Dr. J. C. Babcock of these Laboratories have shown that certain 11-oxo-androstanes undergo addition of methyl Grignard reagent as well as methyllithium to the 11-oxo group.

[7] W. P. Schneider and A.R. Hanze *U.S. Patent* 2,769,823 (November 6, 1956).