synthesis of a greater variety of metal carbonyls, (2) little or no free metal is formed as a by-product, (3) the yields generally are higher, and more sensitive to variations in reaction conditions such as solvent, temperature and pressure, and (4) the product is formed directly as the carbonyl and does not require treatment with water to liberate it.

The method may be exemplified by the synthesis of chromium hexacarbonyl: To a suspension of 4.75 g. (0.030 mole) of anhydrous chromic chloride in 50 ml. of anhydrous diethyl ether was added dropwise a solution containing 28 ml. (0.19 mole) triethylaluminum and 60 ml. of anhydrous diethyl ether over a period of 30 minutes at 0° under Seaford grade nitrogen. The mixture then was charged into a 250-ml. Magne-Dash autoclave in a dry nitrogen box. The autoclave was purged twice with 600 p.s.i.g. C.P. grade carbon monoxide and pressurized with 3500 p.s.i.g. of carbon monoxide. The autoclave then was heated with stirring at 100–115° for 5.5 hours. After the autoclave had cooled overnight to room temperature, it was vented slowly at −80°. The reaction mixture was quenched carefully at 0° under a Dry Ice condenser with a methanol–benzene solution, water, and hydrochloric acid in succession. Finally, the mixture was steam distilled with stirring, and 5.0 g. (76% yield) of chromium hexacarbonyl, m.p. 154–155° (uncor.), was obtained.

Details of this method as it applies to the synthesis of various metal carbonyls will be reported in a future paper.

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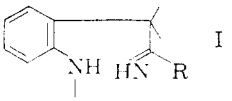
RECEIVED AUGUST 20, 1958

SIX-MEMBERED RING FORMATION DURING FISCHER INDOLE SYNTHESIS

Sir:

The Robinson mechanism for the Fischer indole synthesis[1] has received strong confirmation recently. Carlin, *et al.*,[2] have presented convincing evidence for the detailed intermediates involved in the rearrangement and, in particular, the existence of an intermediate of type I has been established by its isolation in two instances.

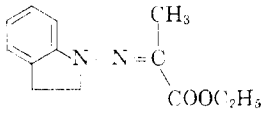


I

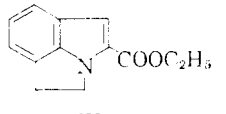
Plieninger[3] obtained such an intermediate from the Fischer reaction with α-keto-γ-butyrolactone phenylhydrazone, and Suvorov, *et al.*,[4] trapped the intermediate aniline in the rearrangement of butanone phenylhydrazone.

As a consequence of the existence of intermediate I, it should be possible, in any appropriately constituted molecule wherein five-membered indole ring formation is difficult and where R is a suitably reactive group, to have ring closure take an alternative course and form the six-membered ring. This result has been realized for the first time with the hydrazone (II) from 1-aminoindoline and ethyl pyruvate. On being subjected to conditions of the Fischer reaction, II formed the 3-hydroxy-2-quinolone III as the major product.[5] In addition there was isolated a small amount of the indole IV, containing the heretofore unknown pyrrolo[3,2,1-h,i]indole ring system.[6]

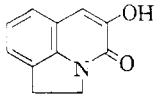
The hydrazone II (m.p. 87–87.5°) was heated



II



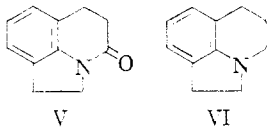
IV



III

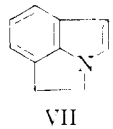
for six hours in absolute ethanol containing 10 volume per cent. sulfuric acid, and cooling the reaction mixture led to crystallization of the hydroxyquinolone III (m.p. 241°. *Anal.* Found: C, 70.7; H, 4.8; N, 7.7; equiv. wt., 191). From the mother liquors, by chromatography on alumina, α-carbethoxyindole IV was isolated (m.p. 74–74.5°. *Anal.* Found: C, 72.8; H, 6.2; N, 6.3; OC_2H_5, 20.6).

The 3-hydroxy-2-quinolone structure was assigned to III on the basis of its analysis and characteristic ultraviolet spectrum.[7] It was established beyond question by Wolff–Kishner reduction of III to the quinolone V (m.p. 112–113°. *Anal.* Found: C, 76.3; H, 6.1; N, 7.9) and reduction of the latter with lithium aluminum hydride to lilolidine (VI).[8]



V

VI



VII

VIII

(1) G. M. and R. Robinson, *J. Chem. Soc.*, **113**, 639 (1918); **125**, 827 (1924).

(2) R. B. Carlin and G. W. Larson, THIS JOURNAL, **79**, 934 (1957); R. B. Carlin and D. P. Carlson, *ibid.*, **79**, 3605 (1957); R. B. Carlin, W. O. Henley, Jr., and D. P. Carlson, *ibid.*, **79**, 5712 (1957).

(3) H. Plieninger, *Ber.*, **83**, 273 (1950); H. Plieninger and I. Nogradi, *ibid.*, **88**, 1964 (1955).

(4) N. N. Suvorov, N. P. Sorokina and Y. N. Scheinker, *Khim. Nauka i Prom.*, **2**, 394 (1957).

(5) Quinolones have been observed in the Diels–Reese reaction [O. Diels and J. Reese, *Ann.*, **511**, 168 (1934); E. H. Huntress, J. Bornstein and W. H. Hearon, THIS JOURNAL, **78**, 2225 (1956)] when the 1:1 adducts of hydrazobenzenes and dimethyl acetylenedicarboxylate were heated in picoline. These adducts gave pyrazolones with acid, and in two cases out of four gave indoles on heating in xylene. Although this reaction may involve intermediates similar to those in the Fischer reaction, further clarification is needed on the striking effect of solvent and the failure of two of the adducts to yield indoles.

(6) The claim of J. G. Jackson and J. Kenner, *J. Chem. Soc.*, 573 (1928), to have prepared this ring-system was shown to be incorrect by G. K. Hughes, F. Lions and E. Ritchie, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 209 (1938), and H. G. Dunlop and S. H. Tucker, *J. Chem. Soc.*, 1945 (1939).

(7) R. G. Ault, E. L. Hirst and R. A. Morton, *ibid.*, 1653 (1935); K. G. Cunningham and G. G. Freeman, *Biochem. J.*, **53**, 328 (1953); A. Bracken, A. Pocker and H. Raistrick, *ibid.*, **57**, 587 (1954).

(8) B. D. Astil and V. Boekelheide, *J. Org. Chem.*, **23**, 316 (1958).

The structure of the α-carbethoxyindole IV was established by saponification to the acid (m.p. 262°. *Anal.* Found: C, 70.8; H, 4.9; N, 7.3; equiv. wt., 188) and decarboxylation to 1,2-dihydropyrrolo[3,2,1-h,i]indole (VII) (m.p. 76–77°. *Anal.* Found: C, 83.8; H, 6.1; N, 9.6). In each case, the ultraviolet absorption was typical for a substituted indole and practically identical with that of the corresponding compound of the six-membered ring series (VIII).[9]

(9) G. Barger and E. Dyer, THIS JOURNAL, **60**, 2414 (1938).

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RECEIVED JULY 28, 1958

A DIFFERENCE IN BOVINE AND HUMAN FIBRINOPEPTIDES WITH RESPECT TO THE OCCURRENCE OF TYROSINE-O-SULFATE

Sir:

Bettelheim[1] has reported tyrosine-O-sulfate to be a component of fibrinopeptide B, one of the peptides liberated by the action of thrombin on bovine fibrinogen. Recently Blombäck and Vestermark[2] also have reported evidence for the presence of tyrosine-O-sulfate in bovine fibrinopeptide B.

We have confirmed the presence of a component with the properties of tyrosine-O-sulfate in fibrinopeptide of bovine origin but have been unable to detect this compound in peptide derived from human fibrinogen.

Our initial experiments with bovine fibrinopeptide appeared to indicate the presence of a component, readily hydrolyzed by acid, but yielding a product other than tyrosine. The source of these difficulties proved to be the large amount of carbohydrate impurities in clinical thrombin (bovine origin, Parke, Davis and Co.). This material on acid hydrolysis yielded ultraviolet absorption maxima at 283 and 286 mμ in acid and alkaline solution, respectively, which is believed to be due to formation of hydroxymethylfurfural. These reactions either completely obscured or destroyed the liberated tyrosine. Purification of the thrombin according to Rasmussen[3] on Amberlite XE-64 (Rohm and Haas Co.) resulted in removal of interfering materials and a high purity thrombin.[4] Bovine fibrinogen was purified by the procedure of Laki[5] and was 94–96 per cent. clottable. Fibrinopeptide was isolated by the procedure of Bettelheim[6] using purified thrombin. The resulting fibrinopeptide mixture possessed the properties described by Bettelheim[1] with respect to ultraviolet spectra before and after acid hydrolysis. Chromatography of a barium hydroxide hydrolysate of fibrinopeptide on Dowex 1 acetate yielded a peak corresponding in position to that of synthetic tyrosine-O-sulfate.

(1) F. R. Bettelheim, THIS JOURNAL, **76**, 2838 (1954).
(2) B. Blombäck and A. Vestermark, *Arkiv for Kemi*, **12**, 173 (1958).
(3) P. S. Rasmussen, *Biochim. Biophys. Acta*, **16**, 157 (1955).
(4) W. H. Seegers and W. G. Levine, *Seventh Ann. Symposium on Blood*, Wayne State University, Detroit, 1958.
(5) K. Laki, *Arch. Biochem.*, **32**, 317 (1951).
(6) F. R. Bettelheim, *Biochim. Biophys. Acta*, **19**, 121 (1956).

Electrophoresis at *p*H 4.1, using the procedure of Bettelheim,[6] yields two bands with peptide of both bovine and human origin. The mixture of fibrinopeptides isolated from human fibrinogen purified with ammonium sulfate according to Laki[5] or with alcohol according to Morrison, *et al.*,[7] has shown no spectral evidence for tyrosine either before or after mild acid hydrolysis.

Other investigators[8–11] have shown that bovine fibrinogen possesses N-terminal glutamic acid and tyrosine while human fibrinogen possesses N-terminal alanine and tyrosine. The observations reported here suggest that other differences in chemical composition exist in fibrinogen of bovine and human origin.

Acknowledgments.—This investigation has been aided by grants from the Graduate School Research Fund of the University of Minnesota, the Eli Lilly Co. and the Life Insurance Medical Research Fund. Human fraction I was supplied through the courtesy of the American Red Cross and E. R. Squibb and Sons. The assistance of Robert Eric Olson, Robert Kyle and Miss Charlotte Rothnem in preparation of purified thrombin, fibrinogen and synthetic tyrosine-O-sulfate is gratefully acknowledged.

(7) P. R. Morrison, J. T. Edsall and S. G. Miller, THIS JOURNAL, **70**, 3103 (1948).
(8) K. Bailey, F. R. Bettelheim, L. Lorand and W. R. Middlebrook, *Nature*, **167**, 233 (1951).
(9) L. Lorand and W. R. Middlebrook, *Biochem. J.*, **52**, 196 (1952).
(10) L. Lorand and W. R. Middlebrook, *Science*, **118**, 515 (1953).
(11) B. Blombäck, *Arkiv for Kemi*, **12**, 299 (1958).
(12) Fellow of the Helen Hay Whitney Foundation, New York, N. Y., deceased, January 16, 1958.

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RECEIVED AUGUST 12, 1958

A NEW PROCEDURE FOR FORMING CARBON-CARBON BONDS[1]

Sir:

In connection with our studies in oxindole chemistry[2] we have uncovered a novel method of monoalkylation of active methylene compounds. An investigation of a new synthesis of oxindole (Ia) by a desulfurization of isatin ethylenethioketal (II), m.p. 200–201° (Found: C, 53.92; H, 4.17; N, 6.50) revealed that a Raney nickel treatment of II in benzene or for four hours in ethanol gave the desired product. However, longer runs with W-2 Raney nickel and II, or even Ia, in a 10:1 weight ratio, in various alcoholic solutions yielded 3-alkyloxindoles (I).

Table I illustrates that (a) oxindole is an intermediate in the conversion of II to Ib-d; (b) a primary alcohol reacts faster than a secondary carbi-

(1) This work was supported by a research grant from the National Institutes of Health, Public Health Service, Department of Health, Education and Welfare (M1301).
(2) *Cf.* E. Wenkert, B. S. Bernstein and J. H. Udelhofen, THIS JOURNAL, **80**, 4899 (1958).