Tetrahedron Letters No.40, pp. 4849–4853, 1966. Pergamon Press Ltd.
Printed in Great Britain.

THE STRUCTURE OF A YELLOW SUBSTANCE FORMED BY MILD OXIDATION OF AMINOPYRINE

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(Received 12 July 1966; in revised form 23 July 1966)

The yellow substance, which slightly formed as a by-product in case of preparation of a molecular compound (1) for an analgesic antifebrile by fusion of aminopyrine, namely, 2,3-dimethyl-4-dimethylamino-1-phenylpyrazolin-5-one (I) with secobarbital or barbital in the presence of air, was also obtained by mild oxidation of (I) with air in a poor yield. Structural elucidation by chemical and physical methods was carried out, leading to confirmation of the formula (II) for the above yellow substance.

At first, a fused mixture of (I) and secobarbital was kept in a sealed tube in the presence of air and heated on a water-bath, the mixture colouring yellow. On the other hand, the above mixture was treated as above in the presence of nitrogen, giving no coloured substance. These facts suggest that the influence of oxygen in the air is one of the important factors for colcuration.

These results also seem to coincide with the report that the pyrabital prepared in a current of carbon dioxide was colourless (2). Furthermore, it is well known that the compound (I) is changed to yellow on exposure to the air. With regards to the oxidation products of aminopyrine (I) several studies (3,4,5) have hitherto been achieved, but all of them were completely different from our yellow substance.

When a mixture of one mole of (I) and an equivalent molar amount of secobarbital or barbital was heated on a water-bath for one hour, yellowish products were formed. Thin-layer chromatography using ether-ethyl acetate (1:2) as solvent showed a yellow spot of R_F 0.76 besides the spots of (I) and secobarbital or barbital. Furthermore, the same treatment of an equivalent molar amount of (I) and benzoic acid or salicylic acid also afforded the same yellow spot as above at R_F 0.76 on its thin-layer chromatogram.

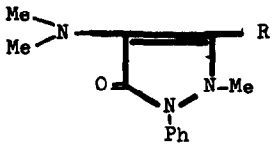
Oxidation of (I) with potassium permanganate, hydrogen peroxide solution, selenium dioxide, ferric chloride, and chromic anhydride, was examined in order to obtain a large amount of (II), but separation of many products by thin-layer chromatography resulted in failure. Therefore, the formation of the yellow substance on introducing the air into a heated solution of (I) in various solvents, was investigated. Among them, ethanol, acetic acid, and acetic anhydride were found to be suitable for the formation of yellow substance.

For instance, a solution of (I) (100 g.) in acetic acid was heated on a water-bath for 12 hours, during which time the air was violently introduced. After the reaction, removal of the solvent under reduced pressure gave the residue, which was basified with 10 % sodium hydroxide solution and filtered. The preceding filtrate was extracted with ethyl acetate. Removal of the extract gave the crude yellow substance.

Preparative thin-layer chromatography and recrystallisation from petroleum ether gave the compound (II) (2 g.) as yellow prisms, m. p. 67 ~ 69° (Found: C, 64.05; H, 6.36; N, 17.22. $C_{13}H_{15}N_3O_2$ requires C, 63.66; H, 6.16; N, 17.13 %), which was also characterized as its semicarbazone (III). Recrystallisation of (III) from isopropyl alcohol gave yellow prisms, m. p. 217 ~ 219° (decomp.) (Found: C, 56.09; H, 6.22; N, 27.38. $C_{14}H_{18}N_6O_2$ requires C, 55.61; H, 6.00; N, 27.80 %). Furthermore, reduction of (II) with sodium borohydride gave the alcohol derivative (IV) which was recrystallized from benzene-ligroin to give colourless prisms, m. p. 141 ~ 142° (Found: C, 62.95; H, 6.77; N, 16.98. $C_{13}H_{17}N_3O_2$ requires C, 63.14; H, 6.93; N, 16.99 %).

The infrared spectrum (in KBr) of (II) showed maxima at 1670 (formyl C=O), 1630 (lactam C=O), and 1610 cm.$^{-1}$ (double bond, >C = C< , broad). On the other hand, the former characteristic formyl band disappears in case of the alcohol derivative (IV), only the lactam band remains at 1640 cm.$^{-1}$, and a hydroxy band appears at 3300 cm.$^{-1}$ The ultraviolet spectrum of (II) in water

showed maxima at 315 mμ (log ε 3.65) and 389 mμ (log ε 4.03), but that of (II) in 0.1 N hydrochloric acid solution showed maxima at 265 mμ (log ε 3.96), the latter of which is closely similar to the spectra of (I) and (IV) in water. The high-frequency band at 389 mμ seems to be related to deep yellowish colour. The NMR spectrum (in $CDCl_3$) of (II) showed the protons (3H) of 2-methyl group at 2.89 p.p.m., one formyl proton at 9.95 p.p.m. and protons (6H) of 4-dimethylamino-group at 3.33 p.p.m.



I : R = Me
II : R = CHO
III : R = CH=NNH-$CONH_2$
IV : R = CH_2OH

Since oxidation of the methyl group with air to form heterocyclic aldehyde has not yet been described, this reaction seems to be very interesting from the point of the purity of aminopyrine.

Acknowledgement. We thank President A. Yanagisawa and Mr. O. Takagi, Grelan Pharmaceutical Co. Ltd. for their grateful assistance.

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